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VOLUME 70  
1942

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.





# CONTENTS OF VOLUME 70

JULY 1942. NUMBER 1

	PAGE
Transfusion of Conditioned Universal Blood: Clinical Observations. Niels C. Klendshøj, M.D.; Crichton McNeil, M.D.; Paul Swanson, M.D., and Ernest Witebsky, M.D., Buffalo.....	1
Refractory Hemolytic Anemia: A Report of Five Cases in Which Treatment Was with Splenectomy. John C. Sharpe, M.D., and J. Perry Tollman, M.D., Omaha.....	11
Acute Coronary Thrombosis in Industry: I. Direct Nonpenetrating Injuries, with Report of Cases. Harry D. Leinoff, M.D., New York.....	33
Stenosis of the Infundibulum. Maurice Lev, M.D., and Sidney Strauss, M.D., Chicago .....	53
Renal Function in Diabetes Insipidus. Nahum J. Winer, M.D., Boston.....	61
Acute Disseminated Lupus Erythematosus, Without Cutaneous Manifestations and With Heretofore Undescribed Pulmonary Lesions. Harold L. Rakov, M.D., and J. Spottiswood Taylor, M.D., Kingston, N. Y.....	88
Uric Acid Partition in Gout and in Hepatic Disease. David Adlersberg, M.D.; Edith Grishman, M.D., and Harry Sobotka, Ph.D., New York....	101
Multiple Polyps of the Esophagus: Report of a Case with Complicating Recurrent Gastrointestinal Hemorrhages. R. Dickes, M.D.; A. F. Knudsen, M.D., and S. C. Franco, M.D., Brooklyn.....	121
Progress in Internal Medicine:	
Infectious Diseases: A Review of Significant Publications in 1941-1942. Hobart A. Reimann, M.D., Philadelphia.....	132
News and Comment.....	178
Book Reviews.....	179

AUGUST 1942. NUMBER 2

Staphylococcic Pneumonia Occurring During an Epidemic of Influenza. Maxwell Finland, M.D.; Osler L. Peterson, M.D., and Elias Strauss, M.D., Boston.....	183
Exophthalmos in Patients with Various Types of Goiter. Mayo H. Soley, M.D., San Francisco.....	206
Unusually High Insulin Requirements in Diabetes Mellitus: Report of a Case. William I. Glass, M.D.; Clifford L. Spingarn, M.D., and Herbert Pollack, M.D., New York.....	221
Neuropsychiatric Disturbances in Internal Disease: Metabolic Factors and Electroencephalographic Correlations. George L. Engel, M.D., Cincinnati, and Sydney G. Margolin, M.D., New York.....	236
Vascular Phase of Chronic Diffuse Glomerulonephritis: A Clinicopathologic Study. Henry Horn, M.D.; Paul Klemperer, M.D., and Morris F. Steinberg, M.D., New York.....	260

AUGUST—*Continued*

PAGE

Pyelonephritis and Hypertension: A Study of Their Relation in 11,898 Necropsies. Norman M. Shure, M.D., Chicago.....	284
Intermittent Fever of Unknown Origin: Recurrent High Fever with Benign Outcome in a Patient with Migraine and Notes on "Neurogenic" Fever. Stewart Wolf, M.D., and Harold G. Wolff, M.D., New York.....	293
Progress in Internal Medicine:	
Diseases of the Heart: A Review of Significant Contributions Made During 1941. Ashton Graybiel, M.D., with the Editorial Assistance of Paul D. White, M.D., Boston.....	303
News and Comment.....	343
Book Reviews.....	345

## SEPTEMBER 1942. NUMBER 3

Mortality in Diabetic Coma. Morris F. Collen, M.D., Berkeley, Calif.....	347
Interrelation of the Factors Influencing Mortality in Diabetic Coma: A Statistical Study. Morris F. Collen, M.D., Berkeley, Calif.....	369
Experimental Production of Emphysema. Richard A. Rasmussen, M.D., and W. E. Adams, M.D., Chicago.....	379
Gummatous Aortitis. William H. Gordon, M.D.; Frederic Parker Jr., M.D., and Soma Weiss, M.D., Boston.....	396
Congo Red Test for Amyloid Disease: A Quantitative Technic. Paul H. Harmon, Ph.D., M.D., Sayre, Pa., and Graham Kernwein, M.D., Chicago	416
Utility of the Congo Red Test in Diagnosis and in Differential Diagnosis. Paul H. Harmon, Ph.D., M.D., Sayre, Pa., and Graham Kernwein, M.D., Chicago .....	421
Hodgkin's Disease with Specific Lesions Appearing First in the Skin. Hobart A. Reimann, M.D.; W. Paul Havens, M.D., and Peter A. Herbut, M.D., Philadelphia .....	434
Progress in Internal Medicine:	
Vascular Diseases: Eighth Annual Review. George W. Scupham, M.D., Géza de Takáts, M.D.; Theodore R. Van Dellen, M.D., and Philip L. Marcus, M.D., Chicago.....	444
News and Comment.....	511
Book Reviews.....	512

## OCTOBER 1942. NUMBER 4

Etiology of Atypical ("Virus") Pneumonias, with a Brief Résumé of Recent Discoveries. Hobart A. Reimann, M.D.; W. Paul Havens, M.D., and Alison H. Price, M.D., Philadelphia.....	513
Observed Course of Diabetes Mellitus and Inferences Concerning Its Origin and Progress. Arthur R. Colwell, M.D., Evanston, Ill.....	523
Cinchophen Gastric Ulcers in Chicks. Garnett Cheney, M.D., San Francisco.	532
Treatment of Pneumonia with Sulfathiazole. Alvin E. Price, M.D., and Gordon B. Myers, M.D., Detroit.....	558

OCTOBER—*Continued*

PAGE

Mechanism of Pentothal Sodium Antidiuresis. Herbert Silvette, Ph.D., Charlottesville, Va.....	567
Progress in Internal Medicine:	
Gastroenterology: A Review of the Literature from July 1941 to July 1942. Chester M. Jones, M.D., Boston.....	585
News and Comment.....	686
Book Reviews.....	687

## NOVEMBER 1942. NUMBER 5

Incomplete Rupture of the Aorta: A Heretofore Unrecognized Stage of Dis- secting Aneurysm and a Cause of Cardiac Pain and Cardiac Murmurs. Thomas M. Peery, M.D., Washington, D. C.....	689
Control by Radium of Gastric Acidity. James A. Jenkins, Ch.M. (N.Z.), F.R.C.S., F.R.A.C.S., and Murray McGeorge, M.D. (N.Z.), M.R.C.P., M.R.A.C.P., Dunedin, New Zealand.....	714
Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Measurement of Hemolysis. Edward B. Miller, M.D.; Karl Singer, M.D., and William Dameshek, M.D., Boston.....	722
Function of the Separate Kidneys in Hypertensive Subjects. Herbert Chasis, M.D., and Jules Redish, M.D., New York.....	738
Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids: Clinical Studies. Samuel S. Altshuler, M.D.; Hilda M. Hensel, M.D.; Paul Hecht, M.D., and Richard Pursley, B.S., Eloise, Mich.....	749
Production and Study of Cardiac Failure in Thiamine-Deficient Pigeons. Roy Laver Swank, Ph.D., M.D., and Otto A. Bessey, Ph.D., Boston....	763
Sulfonamide Compounds in Therapy of Bacterial Endocarditis: A Comparison of the In Vitro Inhibitory Effects and the Bacteriostatic Activity. Edward S. Orgain, M.D., and Mary A. Poston, M.A., Durham, N. C.....	777
Anthrax: A Review of Sixty Cases, with a Report on the Therapeutic Use of Sulfonamide Compounds. Herman Gold, M.D., Chester, Pa.....	785
Polymyositis: Report of a Fatal Case. Douglas Goldman, M.D., Cincinnati..	822
Sodium <i>d</i> -Lactate Tolerance as a Test of Hepatic Function. Clarence Cohn, M.D., New York.....	829
Progress in Internal Medicine:	
Syphilis: A Review of the Recent Literature. Frank W. Reynolds, M.D.; Charles F. Mohr, M.D., and Joseph Earle Moore, M.D., Baltimore..	836
Book Reviews.....	916

## DECEMBER 1942. NUMBER 6

Polycythaemia Vera: Report of a Case. Reginald Fitz, M.D.; Burnham S. Walker, M.D., and Charles F. Branch, M.D., Boston.....	919
Clearance of Diodrast, Phenolsulfonphthalein and Inulin in Hypertension and in Nephritis. Thomas Findley, M.D.; Joseph C. Edwards, M.D.; Etta Clinton, and H. L. White, M.D., St. Louis.....	935

DECEMBER—*Continued*

PAGE

Critical Statistical Analysis of Data on Renal Function in Grouped Subjects with Essential Hypertension. James W. Dalton, M.D., and Franklin R. Nuzum, M.D., Santa Barbara, Calif.....	948
Effect of Ulcer on Acidity and Neutralizing Ability in Duodenal Bulb. J. Edward Berk, M.D.; Martin E. Rehfuss, M.D., and J. Earl Thomas, M.D., Philadelphia.....	959
Mercurial and Xanthine Diuretics in Chronic Congestive Heart Failure: A Comparative Survey. Joseph I. Goodman, M.D.; Joseph F. Corsaro, M.D., and Raymond Stacy, M.D., Cleveland.....	975
Hyperactive Vasodepressor Carotid Sinus Reflex. Louis H. Sigler, M.D., Brooklyn .....	983
Roentgen Ray Treatment of Hyperthyroidism. Mayo H. Soley, M.D., and Robert S. Stone, M.D., San Francisco.....	1002
Progress in Internal Medicine:	
Review of Neuropsychiatry for 1942. Stanley Cobb, M.D., Boston.....	1017
Obesity. L. H. Newburgh, M.D., Ann Arbor, Mich.....	1033
News and Comment.....	1097
Book Reviews.....	1098
General Index.....	1099

# ARCHIVES of INTERNAL MEDICINE

VOLUME 70

JULY 1942

NUMBER 1

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## TRANSFUSION OF CONDITIONED UNIVERSAL BLOOD

CLINICAL OBSERVATIONS

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The practice of transfusing blood of group O (IV Moss) to persons belonging to any of the various blood groups is based on the assumption that cells of group O are not hemolyzed or agglutinated by any normal human plasma. The concept of a universal donor as developed by Ottenberg about thirty years ago has had considerable practical application, supported mainly on the theory that the dilution of a donor's blood and the absorption of the isoagglutinins anti-A and anti-B in a patient's plasma and tissue cells would tend to prevent any significant hemolysis or agglutination.

While some institutions with large transfusion services are using blood from universal donors without observing an undue reaction rate, hemolytic and other reactions have been reported after transfusion of such blood. They may vary through all degrees of severity, and a good number of representative cases have been reported in the literature. In an analysis by Gesse<sup>1</sup> in 1935 46 cases of hemolytic reaction were reviewed, of which 20 terminated fatally. Other authors have described severe and fatal reactions. The reports we are referring to do not include transfusion reactions caused by mistakes in determination of the blood groups because of technical errors or because of the presence of subgroups, such as A<sub>2</sub> and A<sub>3</sub>, which had been overlooked. They may,

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1. Gesse, E. R.: Ueber die Verwendung des sogenannter Universalspenders bei der Bluttransfusion, *Deutsche Ztschr. f. Chir.* **245**:371, 1935. Hemolytic Shock After Blood Transfusion, editorial, *J. A. M. A.* **106**:2241 (June 27) 1936.

however, include a limited number of reactions which might have been caused by the newly discovered Rh factor. In some instances, laboratory work has demonstrated high isoagglutinin titers in a donor's blood. Many investigators attributed the cause of the reactions to the interaction between the potent isoantibodies of a donor's plasma and the group-specific components of the cells of a recipient. For this reason the titer of isoantibodies present in universal blood is frequently determined before a transfusion is given.

In this connection the state of New York has adopted an amendment to the Sanitary Code requiring the elimination of the so-called "dangerous" universal donor by such a procedure. Because of these various experiences with universal blood, most clinics today prefer the use of homologous blood for transfusions.

If the presence of high-titered isoantibodies in O blood constitutes the essential objection to the use of the universal blood, their partial or complete neutralization might be attempted. In previous publications<sup>2</sup> it has been shown that adequate reduction in content of isoagglutinins can be accomplished by the addition of small amounts of purified A and B specific substances. Universal blood conditioned in this manner may be considered "safe" from the standpoint of causing hemolysis or agglutination of a recipient's cells.

Because of the complexity of the clinical picture in most of the cases in which a transfusion is needed, a statistical evaluation of reactions to conditioned universal blood as against reactions to untreated O blood and homologous blood is difficult. It would seem that a statistical approach is possible only by comparison of groups of definite clinical entities with carefully selected control groups of similar nature, as the use of the isolated group-specific substances will only prevent reactions caused by the corresponding isoantibodies and not reactions due to other factors, such as those usually defined vaguely as "pyrogens." In other words, from a practical standpoint conditioned universal blood may be considered comparable to homologous blood. At the present time, it is possible to study the results of its use from the standpoint of efficacy of the method and its harmlessness.

As just mentioned, the problem consists in the reduction or elimination from a donor's blood of the anti-A and anti-B isoantibodies. This was accomplished by the addition to the O blood of the blood group-specific substances A and B. These two substances, which define the typing characteristics of all the cells in the body, including the erythro-

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2. Witebsky, E.; Klendshoj, N. C., and Swanson, P.: Reduction or Elimination of the Anti-A Antibody in O Blood by Means of the Addition of the A Specific Substance, *J. Infect. Dis.* **67**:188 (Nov.-Dec.) 1940; Preparation and Transfusion of Safe Universal Blood, *J. A. M. A.* **116**:2654 (June 14) 1941.

cytes, have been made available in recent years. After the investigations of Freudenberg, Landsteiner<sup>3</sup> obtained the A specific substance from horse saliva, and Goebel<sup>4</sup> isolated this material from commercial peptones. Witebsky and Klendshoj<sup>5</sup> obtained an equally potent B substance from gastric juice. Briefly, the procedure of conditioning O blood is carried out as follows<sup>6</sup>:

Blood from a universal donor is collected for transfusion in a vacuum container in the usual manner. This blood may be used immediately, but most specimens are stored in the blood bank. In either case, the A and B substances in physiologic solution of sodium chloride are injected into the blood in the vacuum container and mixed gently for a few minutes before the transfusion is given. Initially, 25 mg. of A substance and 10 mg. of B substance were used arbitrarily in each 500 cc. of O blood. Later, it was found that smaller amounts could be used effectively.<sup>7</sup> There has been no demonstrable harm in using larger quantities, and the attempts to reduce the amounts are being made as a matter of economy. Lower limits have not yet been determined. More A substance than B substance has been used, as the anti-A titer is often found to be higher than the anti-B titer in the same blood. It is of importance that the addition of blood group-specific substances to normal human serum containing the corresponding isoagglutinins does not result in precipitation.

The effect of the group-specific substances has been determined by a comparison of the anti-A and the anti-B titer in each specimen before and after conditioning of the O blood. There is no standardized procedure for the determination of agglutinin titer which permits values from our laboratory to be compared with those of other investigators. The readings reported in this paper were obtained after centrifugation of the tubes and observation of the degree of agglutination macroscopically.

Before we proceed toward a detailed analysis of cases to be presented in this report, the following 2 cases of emergency transfusion may be cited to illustrate the general procedure:

CASE 1.—A steam shovel operator, B. F., aged 56, was accidentally pinned within the cabin of his machine. He was cut free with the aid of torches and

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3. Landsteiner, K.: Note on the Group-Specific Substance of Horse Saliva, *Science* **76**:351 (Oct. 14) 1932.

4. Goebel, W. F.: The Isolation of the Blood Group A Specific Substance from Commercial Peptone, *J. Exper. Med.* **68**:221 (Aug. 1) 1938.

5. Witebsky, E., and Klendshoj, N. C.: The Isolation of the Blood Group-Specific B Substance, *J. Exper. Med.* **72**:663 (Dec.) 1940.

6. In our hospital intravenous therapy, including blood transfusions, is given by members of the department of anesthesia. Dr. Paul Searles, the head of this department, cooperated with us.

7. Part of this material was prepared and made available to us by Eli Lilly & Co.



brought to the hospital in shock. His pulse was rapid and thready. The blood pressure was 54 systolic and 30 diastolic, and his abdomen was rigid. Without blood typing or cross matching, he was given 500 cc. of group O blood with A and B substances added. His blood pressure had increased to 106 systolic and 74 diastolic after the completion of the transfusion. No reactions from the transfusion were observed. He subsequently received 500 cc. of plasma, followed by 1,000 cc. of 5 per cent dextrose in physiologic solution of sodium chloride. The patient was later found to belong to group O, but nevertheless, it is interesting that the transfused O blood had the following high anti-A and anti-B agglutinin titers: anti-A equal to 1:256; anti-B equal to 1:64. After the addition of the A and B specific substances, these titers were determined to be 1:4 for the anti-A isoagglutinins and 1:2 for the anti-B isoagglutinins. The anti-A titer would definitely be considered high. Had the recipient belonged to group A, a serious reaction might have occurred with the use of this blood. The A substance lowered the titer to insignificance.

CASE 2.—The hospital was notified by a private physician that a patient, M. B., whom he had just delivered at home was having a massive postpartum hemorrhage, and a house physician was sent out immediately in the ambulance equipped with a transfusion set and 500 cc. of group O blood to which the A and B substances had been added. The mother was found to be in shock with a low blood pressure and thready pulse. Without typing or cross matching, the prepared blood was infused while the hemorrhage was brought under control. The response was rapid. The estimated blood loss was 1,500 cc. The recipient was never typed. The universal donor's blood was found to contain an anti-A titer of 1:128, which was reduced to 1:2, and an anti-B titer of 1:32, which was reduced to zero. No reaction occurred.

#### REVIEW OF CASES

In the present series of cases a total number of 176 transfusions were given to 147 patients. For twenty-four hours following the completion of a transfusion each patient was under close observation for any subjective or objective signs of reactions, particularly chills, rises in temperature or pulse rate, icterus and hemoglobinuria. The two last-named manifestations were not observed in any case.

Of the total number of transfusions, 123 were given without any observable changes in the patients. The remaining 53 transfusions represent the number to be subjected to analysis. It is impossible to establish criteria which in very ill patients would permit accurate differentiation between reactions to the transfused blood and similar signs due to the illness itself. Perhaps the tabulation of temperature rises over a short period, such as two hours, might tend to exclude, to some degree, the chance rise resulting from the disease, but reliable statistics cannot be based on such arbitrary limits. In each case we have endeavored to evaluate temperature rises over a twenty-four hour period, and we have attributed them to surgical procedures or infectious processes, unless the general temperature pattern of the patient seemed to have undergone a definite change following transfusion.

A total number of 39 transfusions were given which were accompanied by a rise in temperature during the following twenty-four hours and in which we attributed the fever to the patient's general condition and not to the transfusion. These 39 transfusions were given to 34 patients. Increases in temperature were not associated with chills in any case, and in no instance did a significant part of the temperature increase take place during the first two hours following the transfusion. During this period temperature and pulse were recorded every fifteen minutes.

In 24 of these transfusions either the recipient's temperature did not exceed 101 F. at any time during the twenty-four hour period following the transfusion or the difference between the recorded temperature at the

*Maximum Rise in Temperature in the Twenty-Four Hours Following Transfusion of Conditioned Universal Blood*

Blood Group	Case No.	Maximum Temperature Increase, F.	Diagnosis
A	6	2	Amputation of leg; ascending infection
	7	2	Acute appendicitis with perforation
B	8	4.4 and 5.6	Postoperative appendiceal abscess with septicemia; infection of urinary tract and subcutaneous abscess
	9	3.4	Perforated ulcer; diffuse peritonitis
	10	5	Anterior and posterior colporrhaphy and amputation of cervix
	11	1.6	Abscess of abdominal wall
O	12	2.4	Diffuse peritonitis following appendectomy
	13	3.8	Acute cholecystitis after operation; postoperative bronchopneumonia
	14	3	Hysterectomy
	15	4.6	Removal of retroperitoneal tumor
	16	3	Gastric resection; linitis plastica
	17	1.8	Thyroid "storm"
	18	3.8	Gastric resection for adenocarcinoma; atelectasis; obstructive biliary cirrhosis
AB	19	1.4	Postoperative diffuse toxic condition of thyroid

beginning of the transfusion and the maximum temperature during the following twenty-four hours was less than 1 degree (F.). We feel that these transfusions need no further discussion. The remaining 15 transfusions were given to 14 patients who represented the greatest part of the acutely ill patients among the 34 just mentioned. To illustrate the pathologic conditions encountered in these 14 patients, we have tabulated the diagnosis along with the maximum temperature increase over the twenty-four hour post-transfusion period. In 1 case (8) the patient received 2 transfusions, and the increases in temperature in both instances are indicated in the table. These temperature peaks were occurring daily before the patient received his first transfusion and continued for many days after the last transfusion, and they were typical of the fever curve generally seen in this type of infection of the urinary tract.

After deducting from the total the number of cases in which no reaction occurred, in addition to those in which we felt augmented temperatures were part of the normal course of events, there remained 10 cases in which the 14 reactions observed seemed unquestionably to have been precipitated by transfusion. Of these 10 cases, the patients in 5 belonged to blood group A, in 4 to group O and in 1 to group B. It may be stated again that in none of the cases did we observe signs of agglutination or hemolysis. The severity of the temperature reactions had the following distribution: Four transfusions produced temperature increases of between 2 and 4 degrees (F.); in 10 transfusions, the increase exceeded 4 degrees (F.) and chills were present. In the 39 transfusions mentioned previously temperature rises were not associated with chills, while in these 14 transfusions, temperature rises with chills occurred in about two thirds. In all the cases in this group with 1 exception the patients had received multiple transfusions prior to the infusion of universal blood treated with the group-specific substances, and in a number of these cases the transfusions with conditioned universal blood were specifically requested by the attending clinicians as a result of previously encountered reactions.

In cases in which chills occurred during an infusion period the transfusion was stopped immediately. As a rule this took place after the administration of 200 to 300 cc. of blood. In general, the types of reaction which we definitely consider as a direct result of the transfusions were similar in nature, chiefly consisting in increases in temperature and pulse, with associated chills in 10 of the 14 transfusions. It is likely that these reactions were mainly caused by pyrogens. Recent investigations have shown that it is possible to reduce the number of such reactions considerably by eliminating all possible sources of contamination from the transfusion equipment. Rather than to review all details of these 10 cases, it seems desirable to report the following cases to illustrate our general observations:

CASE 3.—A 19 year old girl, R. A., was admitted to the hospital with a six months' history of abdominal cramps and bloody diarrhea. Previous treatment in another hospital had included repeated transfusions. A diagnosis of nonspecific ulcerative colitis was confirmed by roentgen examination, and patchy ulceration was seen through the sigmoidoscope. Her red cell count was 4,100,000, with 76 per cent hemoglobin, and her white cell count was normal. Marked improvement occurred after ileostomy.

The patient's supportive treatment consisted in a number of transfusions and intravenous infusions of sulfanilamide solutions. She was found to belong to group O. Her first transfusion in this hospital caused a chill, a temperature rise of 5.2 degrees (F.) and a pulse rise of 10 after the administration of 250 cc. of homologous O blood without the A and B substances. On each of the following two days she received sulfanilamide solutions intravenously, resulting in temperature increases of 2 and 3 degrees (F.), respectively, and corresponding pulse increases of 30 and

15. One day later she received 500 cc. of universal blood treated with the A and B specific substances, which produced a temperature rise of 2 degrees (F.) but no increase in pulse. She experienced itching of the skin after this transfusion. Three subsequent transfusions without the use of the group-specific substances on three consecutive days gave rises in temperature of 2, 3.5 and 3.2 degrees (F.). Pulse rates remained unchanged. The 3.5 degree rise was associated with a chill.

This case illustrates a typical reaction to transfusions. The neutralization of the isoantibodies in the one specimen of blood treated with group-specific substances would not be of any significance, as the corresponding group-specific antigens, A and B, were not present in the recipient's cells, and there is, of course, no advantage in conditioning universal donor blood if the blood is given to a group O recipient. The conditioning of universal donor blood when given to a group O recipient in our procedure is a matter of routine and not a matter of necessity. The case also affords a demonstration of the similar types of reactions which may follow intravenous infusions of substances other than blood.

CASE 4.—A patient, N. R., was admitted to another Buffalo hospital immediately after hematemesis. Previous history indicated the presence of a peptic ulcer. He had a blood pressure of 80 systolic and 40 diastolic; his pulse rate was 58 per minute, and his temperature was 96.4 F. He belonged to group B. Immediately following admission his red cell count was 4,030,000, with 84 per cent hemoglobin. Five days later the count had dropped to 2,490,000, with 48 per cent hemoglobin. At that time he received 500 cc. of homologous blood, which produced a chill, a temperature rise of 4.2 degrees (F.) and a pulse rise of 30. Two days later the transfusion was repeated with 500 cc. of universal blood neutralized with the A and B substances. This transfusion resulted in a similar reaction. Again the temperature rose 4.2 degrees (F.), with a chill, and the increase in pulse rate was 46. No further complications occurred, and the patient recovered. The anti-A titer in the donor's blood was reduced from 1:16 to 1:2, and the anti-B titer, from 1:8 to zero.

There is a striking similarity in the reactions to the two transfusions. Whatever the explanation is, the isoantibodies may not be considered as offenders, as the titers after neutralization were insignificant, and even the original titers were low enough to place the donor in the low-titered universal group.

The following case is added because it is the only one in which a severe transfusion reaction occurred after the first transfusion using universal blood conditioned with the A and B substances. This case serves as a further illustration of the freakish reaction picture often encountered in multiple transfusions.

CASE 5.—A 36 year old Negress, P. H., had been admitted to the hospital with a bleeding cervical neoplasm. Biopsy had revealed a squamous cell carcinoma, and radium had been implanted. Six months later metastasis had developed. Her red cell count was 2,700,000, with 62 per cent hemoglobin. A severe infection of the urinary tract and rapid loss of weight soon terminated in death. During her last

admission she received 3 transfusions after it had been determined that she belonged to group A. The first transfusion consisted of 500 cc. of universal blood conditioned by the addition of the A and B substances. She reacted with a temperature increase of 2.8 degrees (F.), a chill and a pulse rise of 10. Her next transfusion ten days later, for which homologous blood in the same amount was used, resulted in a temperature rise of 4 degrees (F.) without chill, and a pulse rise of 35. The last infusion of 500 cc. of homologous blood five days later did not cause any reaction.

The universal blood used in the first transfusion had an anti-A titer of 1:256, which was reduced to 1:2. The anti-B titer was 1:128, which was also reduced to 1:2. Ordinarily, the anti-A titer would be considered sufficiently high to be unsafe for transfusion, and this would be particularly true in a patient exhibiting a marked degree of anemia. Although a reaction occurred following this transfusion, no signs ascribable to hemolysis or agglutination appeared.

The question arises as to the possible sensitization in human beings by the preparation used for the conditioning of O blood. Such sensitization might manifest itself if subsequent transfusions would follow the first transfusion after a certain interval. We had several cases in which we gave multiple transfusions of blood containing the A and B substances without observing any trace of clinical sensitization. In some instances we intentionally tried to create optimal conditions for sensitization by allowing an interval of one to three weeks to occur between the first and the second transfusion, without any manifestation of sensitization.

#### COMMENT

The advantages of routine use of universal blood for transfusions cannot be disputed. However, severe and fatal reactions have been reported by a number of investigators as the result of the indiscriminate use of O blood, particularly in cases in which large amounts have been transfused and in which marked anemia was present in the recipients. The danger considered inherent in the use of universal blood is commonly ascribed to the high content of isoantibodies capable of causing hemolysis and agglutination of the recipient's cells—the basis of the term dangerous universal donor.

The method used in the cases reported obviates this danger by partial or complete neutralization of the isoagglutinins with the corresponding purified group-specific substances A and B. It cannot be stressed too much that this procedure can be expected to accomplish just that and that reactions due to other factors will occur from transfusion of such conditioned universal blood as frequently as they are encountered after the use of homologous blood. In the specimens of blood used for transfusions in the cases reported, the average anti-A agglutinin titer was found to be 1:100 and the corresponding anti-B titer

was 1:74. Treatment with A and B specific substances reduced these figures to 1:3 for the anti-A agglutinins and 1:4 for the anti-B agglutinins.

During the practical performance of the reported transfusions a number of points have presented themselves which it seems desirable to discuss. To begin with, we were somewhat apprehensive as to our ability to keep our blood bank sufficiently supplied by O donors. However, our experiences indicate that a cooperative house staff is perfectly capable of procuring an adequate number of universal donors at all times. Our prospective donors are typed immediately when they present themselves to the hospital, and those belonging to group O are selected. The determination of the blood group is done by mixing potent test serum of group A and of group B with the cell suspension under investigation. If an O blood is found, the serum of the donor prepared routinely for serodiagnosis of syphilis is rechecked against known A cells and B cells, which are invariably agglutinated by serum of group O. From the standpoint of economical and efficient operation of the blood bank, it is important that the method described permits us to supply the various hospital services with adequate amounts of blood from a smaller "stock," inasmuch as all the blood available can be used.

Careful judgment should permit one to manage an O blood bank without waste. Another advantageous consequence is that blood may be transfused in a fresher state, as the turnover of the total stock of blood is much more rapid.

The use of conditioned universal blood does away with typing and cross matching as emergency procedures. If universal blood is properly selected and the isoantibodies reduced in strength to within safe limits by the addition of the A and B specific substances, such blood may be given to any recipient without typing and cross matching in an emergency. The only exception to that rule is found in the rare cases of pregnancy in which isoimmunization might have produced an Rh or a similar antibody. In these cases a special type of blood characterized by the absence of the Rh factor is required. We do not advocate the abolishment of cross matching as a routine procedure when it can be done at the leisure of the laboratory personnel, since such a procedure contributes a definite additional safeguard against mistakes.

We have emphasized the use of conditioned universal blood as part of the operation of blood banks, which are now available in most larger hospitals. It is our belief that the use of conditioned universal blood will simplify a blood bank system sufficiently to permit its use in small hospitals. If selection of donors is not an emergency procedure, suitable donors may be determined in small communities by having their blood

typed in qualified laboratories at any distance. Universal donors designated in this manner may contribute their blood to the local blood bank or in individual cases at any time as most desirable.

It is entirely beyond the scope of this paper to discuss the relative merits of transfusion of plasma and of whole blood. When plasma is produced from large pools of blood, the average residual agglutinin titers are likely to be relatively low. If plasma is produced on a small scale from individual specimens of blood, the same considerations may apply as to O blood, and high agglutinin titers can be reduced by the addition of the blood group-specific substances.

#### SUMMARY

Clinical observations on the transfusion of O blood conditioned by the addition of the A and B specific substances are reported. Such blood is characterized by extremely low isoantibody titers and combines the advantages of O blood in regard to the absence of group-specific factors in the cells with the absence of the isoantibodies in the fluid of AB blood.

No reactions ascribable to the combination of transfused isoantibodies with the A and B specific substances of the recipient were observed in 176 transfusions. The A-B mixture used was found to be effective and harmless.

The advantages of the procedure and its relation to the operation of a blood bank with O blood predominantly or exclusively are discussed. Typing of a patient can be eliminated, an important time-saving factor in emergencies. By adopting the method described, it becomes possible for smaller hospitals to maintain a blood bank with O blood exclusively and thus avoid difficulties in keeping blood of all four groups available.

Conditioned universal blood may be kept ready and immediately available for any civil or war emergency.

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# REFRACTORY HEMOLYTIC ANEMIA

## A REPORT OF FIVE CASES IN WHICH TREATMENT WAS WITH SPLENECTOMY

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OMAHA

During the past four years we have been puzzled as to the basic cause and exact classification of a hemolytic type of anemia which we have observed in 5 adults. Furthermore, we were unable to influence the clinical course either by conservative medical treatment or by more radical surgical therapy. Detailed observations have been made in each case before, during and after splenectomy, and we have had the opportunity of making postmortem examinations in 3 cases. Because of the unusual clinicopathologic syndrome, we wish to present our observations and attempt a brief review of the literature and the rather confusing ideas on the subject.

### REPORT OF CASES

CASE 1.—M. H., a white housewife aged 58, was admitted to the University of Nebraska Hospital March 12, 1938 and discharged May 29. For approximately three months before admission the patient had noticed a gradual loss of weight associated with weakness and followed shortly by a "yellow color" of the skin. After the appearance of the jaundice, she had noted anorexia, dizziness and several attacks of nausea and vomiting without colicky pain. She had, however, been subject to mild recurrent epigastric distress following meals, especially after eating fried food. For one month prior to admission she had been aware of some numbness of her fingers but had not noted glossitis or paresthesias of the lower extremities. Though the urine had been dark since the onset of the jaundice, she had not noted any "clay-colored" stools. The past history was nonessential. The family history was entirely irrelevant with regard to any similar disease. While the patient was in the hospital we had the opportunity to study samples of blood from her 2 brothers and 1 sister. There was no evidence of anemia, reticulocytosis, latent jaundice or increased fragility of the red cells.

On physical examination the patient appeared slightly undernourished, with a definite icteric tint to the skin and scleras. A few small hemangiomas were scattered generally over the skin, but no petechiae were present. The eyes, ears and nose were normal. A number of teeth were carious. The tongue was slightly coated but without evidence of papillary atrophy. There was no generalized enlargement of the lymph nodes. Though the heart was not enlarged, a soft

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systolic murmur was heard over the mitral area; the blood pressure was 150 systolic and 72 diastolic. The lungs were clear. The abdomen was not remarkable except that the edge of the liver was palpable 5 cm. below the right costal margin and the spleen was moderately enlarged. The neurologic examination revealed nothing abnormal.

Laboratory examination yielded the following data: The blood count showed a hemoglobin content of 3.9 Gm. per hundred cubic centimeters (23 per cent), 1,200,000 erythrocytes and 2,800 leukocytes, with 23 per cent segmented polymorphonuclears, 1 per cent basophils, 52 per cent lymphocytes and 14 per cent monocytes. The smear showed marked variation in size and shape of the red cells, with a predominance of macrocytes; no spherocytes were seen. Marked polychromasia was apparent, and a few normoblasts were found. The hematocrit determinations showed a mean corpuscular volume of 129 cubic microns, a mean corpuscular hemoglobin content of 44 micromicrograms and a mean corpuscular hemoglobin concentration of 34 per cent. The percentage of reticulocytes was 71.6. The fragility test of the red cells showed beginning hemolysis at 0.46 per cent and complete hemolysis at 0.28 per cent. The bleeding and clotting times were normal; the platelets numbered 284,000. The icterus index of the blood was 55 units. The van den Bergh reaction was direct, positive and immediate, with a quantitative result of 40 mg. per liter. The reaction for urobilinogen in the urine was positive in a dilution of 1:200. The stools gave a negative reaction for occult blood. Analysis of gastric contents showed 14 degrees of free hydrochloric acid and 87 degrees of total acid. The Wassermann reaction of the blood was negative.

Roentgen studies of the gastrointestinal tract failed to show any organic lesions. Studies of the gallbladder showed only a fair concentration of dye with several irregular shadows of negative density lying within the gallbladder, which were interpreted as calculi. Roentgenograms of the long bones showed no gross evidence of any pathologic condition which could account for the anemia.

For three weeks the patient was given large oral and parenteral doses of liver and iron, alone and in combination, without appreciable beneficial effect on the blood count. During this interval the temperature ranged from 99 to 100 F. and the pulse rate from 90 to 100 per minute. The degree of jaundice remained about the same. Since iron and liver were ineffective, they were discontinued, and seven transfusions totaling 3,235 cc. of blood were given during the next two weeks. The blood counts during this interval ranged from 3.4 to 6.8 Gm. of hemoglobin per hundred cubic centimeters, 660,000 to 1,800,000 red cells and 5,200 to 8,000 white cells. The differential count continued to show the same pattern as on admission. The percentage of reticulocytes varied from 80 to 90. The icterus index continued to fluctuate between 40 and 55 units. The hematocrit determinations showed the same macrocytic tendency.

Because the patient failed to respond to active medical treatment, splenectomy was performed April 20, with the patient under spinal anesthesia. The spleen after removal weighed 552 Gm. Except for slight hepatic enlargement and the presence of cholelithiasis, no significant pathologic evidence was found to account for the persistent hemolytic anemia. After operation the patient had an uneventful clinical convalescence. However, the blood count failed to respond to splenectomy in any way comparable to that seen in patients with familial hemolytic jaundice.<sup>1</sup>

1. Sharpe, J. C.; McLaughlin, C. W., Jr., and Cunningham, R.: Hemolytic Jaundice: Immediate and Delayed Changes in the Blood After Splenectomy, *Arch. Int. Med.* 64:268-279 (Aug.) 1939.

Therefore, four additional transfusions totaling 1,680 cc. of blood were given during the five weeks following operation. When the patient was dismissed from the hospital five weeks after splenectomy, the blood count showed a hemoglobin content of 8 Gm. per hundred cubic centimeters (47 per cent), 2,600,000 red cells and 10,600 white cells. Reticulocytosis (66 per cent) was still evident. The icterus index was 25 units. Though the patient remained moderately jaundiced, she felt rather definitely improved in general strength.

The patient returned to the outpatient department on Feb. 8, 1939, ten months after removal of the spleen. She still complained of persistent weakness. The hemoglobin content was 8.6 Gm. per hundred cubic centimeters (51 per cent); the red cell count, 2,120,000, and the white cell count, 9,100, with 55 per cent segmented forms, 16 per cent staff forms, 20 per cent lymphocytes, 4 per cent basophils and 5 per cent monocytes. The blood smear showed occasional Howell-Jolly bodies, rare nucleated red cells, moderate anisocytosis, marked polychromatophilia with basophilic stippling and achromia. No spherocytes were seen in the smear. Hematocrit determinations showed a mean corpuscular volume of 143 cubic microns, a mean corpuscular hemoglobin content of 40.5 micromicrograms and a mean corpuscular hemoglobin concentration of 28.3 per cent. The icterus index of the blood was 19 units. The platelets numbered 720,000. The percentage of reticulocytes was 24. The erythrocyte fragility test showed beginning hemolysis at 0.52 per cent and complete hemolysis at 0.28 per cent.

Thirteen months after splenectomy the patient's family physician reported she had gained in strength and weight, but that her anemia persisted. The hemoglobin content was 12.7 Gm. per hundred cubic centimeters (75 per cent); the erythrocyte count, 3,750,000, and the leukocyte count, 7,500.

*Pathologic Observations.*—The spleen weighed 552 Gm. It was of essentially normal shape, and the cut surface showed nothing particularly unusual.

Sections show trabeculae approximately normally arranged. The lymphoid follicles are few in number and are small, usually without reaction centers. There is extensive pigmentation. Part of this pigment lies within the phagocytes, but some seems to lie free in the intercellular spaces. The sinusoids contain numerous large phagocytes, and there is occasional red cell phagocytosis. Reticulum cells are proliferating, and their differentiation can be followed to the production of free phagocytes. Scattered through the tissue are large numbers of polymorphonuclear neutrophils. These are all relatively mature. Eosinophils are present in moderate numbers. Nucleated red cells are present in large numbers. These are frequently arranged in clusters which show varying stages of maturity.

Bone marrow obtained by sternal aspiration was studied before and after operation. Before operation 78 per cent of the nucleated forms in the bone marrow were normoblasts. After operation the percentage of normoblasts decreased to 43, with a corresponding rise in the more mature forms of neutrophils. No abnormal cell forms were encountered.

CASE 2.—E. M., a married white woman aged 60, entered the University of Nebraska Hospital Nov. 29, 1936 and was dismissed Jan. 19, 1937. For three months prior to admission the patient had complained of epigastric distress associated with periodic attacks of nausea, vomiting, progressive weakness and a loss of 25 to 30 pounds (11 to 14 Kg.) in weight. The patient had been studied in the outpatient department, and a tentative diagnosis of carcinoma of the stomach had been made. She was placed on oral iron and liver therapy, without beneficial

effect. The patient stated she had not had any previous illness of a serious nature, and the family history was noncontributory with regard to any similar disease.

On physical examination the patient presented slight pallor and icterus of the skin. The temperature and the pulse and respiration rates were normal. The eyes, ears, nose and throat were normal. There was no generalized lymphadenopathy. The lungs were clear. The heart was normal except for a slight systolic murmur at the apex; the blood pressure was 108 systolic and 70 diastolic. The abdomen was pendulous, with a large ventral hernia. In addition, a large mass was present in the upper left quadrant of the abdomen which extended from the xyphoid process to a point 5 cm. below the umbilicus and which was interpreted as the spleen. Neither the pelvic examination nor the neurologic examination revealed anything abnormal.

The blood count showed a hemoglobin content of 11.9 Gm. per hundred cubic centimeters (70 per cent), with 4,650,000 red cells and 2,800 white cells. The differential count showed 48 per cent segmented forms, 10 per cent staff forms, 40 per cent lymphocytes and 2 per cent monocytes. The percentage of reticulocytes varied from 0.1 to 0.4 per cent. The fragility test of the red cells showed beginning hemolysis at 0.44 per cent and complete hemolysis at 0.26 per cent. Hematocrit studies revealed a mean corpuscular volume of 77 cubic microns, a mean corpuscular hemoglobin content of 23 micromicrograms and a mean corpuscular hemoglobin concentration of 30 per cent. The icterus index of the blood was 16 units, and the van den Bergh reaction was direct and immediate. The reaction for urobilinogen in the urine was positive in a 1:40 dilution. The stools were highly colored with bile, yet the reaction for occult blood was negative. The bleeding time was two minutes, and the clotting time, eighteen minutes. The platelets on several examinations ranged from 104,000 to 238,000. Both the galactose tolerance and the bromsulphalein tests for hepatic function yielded normal results. Analysis of gastric contents disclosed a normal amount of free hydrochloric acid.

Roentgenograms of the gallbladder were interpreted as giving evidence of cholecystitis with cholelithiasis. Roentgen studies of the gastrointestinal tract showed a large mass in the left upper quadrant of the abdomen that extended from the diaphragm to the iliac crest, which was interpreted as an enlarged spleen. A pneumoperitoneum was produced by injecting 2,200 cc. of carbon dioxide into the peritoneal cavity. The mass was easily visualized and again was interpreted as an enlarged spleen.

One month after admission to the hospital splenectomy was performed by Dr. Herbert Davis with the patient under general anesthesia. The spleen, weighing 1,700 Gm., was found to be covered with adhesions and was removed with difficulty. The liver was grossly normal in appearance, whereas the gallbladder was adherent and thickened and contained calculi. After the operation a transfusion of 500 cc. of whole blood was given. The patient had an uneventful convalescence and was dismissed from the hospital on the twenty-first day after operation, at which time the blood count showed a hemoglobin content of 11.7 Gm. per hundred cubic centimeters (69 per cent), 4,300,000 red cells and 12,300 white cells. At this time the percentage of reticulocytes was 0.5; the icterus index was 16; the bleeding and clotting times were normal; the platelets numbered 324,000, and the hematocrit reading and the results of the fragility test were essentially the same as on admission.

The patient was readmitted to the hospital Feb. 26, 1938, approximately one year later, complaining of severe recurrent pains in the upper right quadrant of the abdomen associated with jaundice. These attacks were interpreted as typical

of obstructive cholelithiasis. Except for these episodes of pain, her general condition had apparently improved. The results of physical examination were not essentially different from those of the previous examination. The hemoglobin content was 14.6 Gm. per hundred cubic centimeters (86 per cent); the erythrocyte count, 4,950,000, and the leukocyte count, 10,100. The differential count was within normal limits. The percentage of reticulocytes was 2.2. The icterus index was 10 units, and the van den Bergh reaction was direct. The platelet count and the bleeding and coagulation times were normal.

Cholecystectomy was performed on March 4, at which time marked technical difficulty was encountered because of the amount of adhesions around the gall-bladder and a rather marked tendency to bleeding. Though the patient's immediate postoperative course was uneventful, during the following six weeks she underwent several severe internal hemorrhages, accompanied by profound shock, and required four blood transfusions. Persistent postoperative hemorrhage finally led to death on April 19.

*Pathologic Observations.*—The spleen weighed 1,700 Gm. It was normal in gross contour. The section shows numerous well formed lymphoid follicles, usually with definite reaction centers. Eosinophils are present in considerable numbers. There is appreciable reticulum cell proliferation, with the formation of many free phagocytes within the sinusoids, but there is no accumulation into definite collections. Occasional normoblasts are seen, but no erythropoietic fossae are encountered. No phagocytosis of red cells is seen.

*Autopsy.*—Death occurred sixteen months after splenectomy and shortly after cholecystectomy. External examination showed a sinus tract in the right upper quadrant of the abdomen penetrating it deeply and communicating with the gall-bladder bed and the common duct region. This was walled off from the general peritoneal cavity by relatively firm adhesions. The heart, lungs and gastrointestinal tract generally were normal in appearance except for the presence of a considerable amount of fresh and partly digested blood in the small bowel. The cystic artery opened into the bottom of the sinus tract, as did the common bile duct. This permitted the escape of blood into the gastrointestinal tract. The liver was rather soft, and sections showed extensive fatty degeneration. The lymph nodes from several areas showed no abnormalities. No studies of the bone marrow were done.

CASE 3.—M. B., a housemaid aged 25, entered the University of Nebraska Hospital for the third time Nov. 30, 1936, with symptoms of a severe crisis of hemolytic anemia. On the two previous admissions, four years before, she had been in similar crises with a red cell count of about 1,000,000. Symptoms of increasing weakness, yellowish pallor and bouts of diarrhea had been present for two months.

On physical examination the patient was extremely pale and moderately jaundiced. The temperature was 101.6 F.; the pulse rate, 120 per minute, and the blood pressure, 108 systolic and 62 diastolic. There were no purpuric manifestations on the skin, and the flicking test gave a negative result. There was no glossitis or papillary atrophy of the tongue. Generalized lymphadenopathy was absent. There were no pulmonary abnormalities. There was a soft systolic murmur at the apex. The spleen was enlarged and was palpable 4 cm. below the left costal margin. The neurologic examination revealed nothing abnormal.

At the time of admission the hemoglobin content was 3.4 Gm. per hundred cubic centimeters (20 per cent); the erythrocyte count, 990,000, and the leukocyte count, 4,000. Except for a shift to the left of the polymorphonuclear series, the

differential count was normal. The blood smear showed extreme variation in the size and shape of the red cells, with numerous polychromatophilic cells, Cabot rings and Howell-Jolly bodies. The mean corpuscular volume of the erythrocytes was 103 cubic microns; the mean corpuscular hemoglobin content was 36 micro-micrograms. The bleeding, clotting and clot retraction times were normal; the number of platelets was slightly reduced. The percentage of reticulocytes was 5.5. The fragility test of the red cells showed beginning hemolysis at 0.46 per cent and complete hemolysis at 0.28 per cent. The icterus index was 27 units; the van den Bergh reaction was indirect, with a quantitative result of 2 mg. per liter. The reaction for urobilinogen in the urine was positive in a dilution of 1:60. There was complete absence of free hydrochloric acid in the gastric contents, and examination of the stool did not reveal any blood. The urine was normal, and the Wassermann reaction of the blood was negative. A biopsy of the bone marrow showed marked hyperplasia of the erythropoietic tissue. Roentgenograms of the skull showed definite evidence of increased thickness.

The patient was critically ill. Emergency splenectomy was considered, but transfusions were elected in view of the extremely low blood counts and the poor operative risk. A transfusion of 450 cc. of whole blood by the indirect citrate method was given on each of two successive days. Though there was no immediate febrile reaction after either transfusion, a few hours after the second one the patient complained of severe abdominal pain. The jaundice became more intense, and the spleen became tender and increased in size. The temperature gradually rose to 105.4 F. During the next twenty-four hours the erythrocyte count dropped from 1,700,000 to 1,360,000 and the hemoglobin concentration from 36 to 25 per cent. The donor and recipient bloods were rematched and found to be compatible. The patient was watched carefully for signs of renal damage, but no anuria, hematuria or hemoglobinuria developed. Four days later splenectomy was performed with the patient under gas-ether anesthesia, with prompt improvement in the blood and progressive decrease of the jaundice. Two months later the gallbladder was removed because of cholelithiasis. The patient was discharged from the hospital in a greatly improved state, both clinically and hematologically.

The patient reported for a check-up examination one year after splenectomy, at which time she felt moderately improved. There were still a definite pallor and mild icterus of the skin. The hemoglobin content at this time was 7.82 Gm. per hundred cubic centimeters (46 per cent); the red cell count, 2,630,000, and the white cell count, 13,100. The differential smear was normal. The percentage of reticulocytes was 8.7. The erythrocyte fragility test showed beginning hemolysis at 0.56 per cent and complete hemolysis at 0.20 per cent. Though we have had no further opportunity personally to study the patient in detail, she recently reported from her home on the west coast that she has continued to have spells of poor health and fatigue, in spite of persistent oral and parenteral liver and iron therapy. Her last blood count, in June 1940, three and one-half years after splenectomy, showed a hemoglobin content of 11.90 Gm. per hundred cubic centimeters (70 per cent), 4,000,000 erythrocytes and 11,000 leukocytes, with 52 per cent polymorphonuclears, 47 per cent lymphocytes and 1 per cent eosinophils.

*Pathologic Observations.*—The spleen weighed 960 Gm. and was normal in shape. The cut surface showed rather extensive yellow stippling.

On section the lymphoid follicles are small and rather widely spaced, and only a few show definite reaction centers. There is considerable hyperplasia of

reticular cells, and stages of differentiation to the development of free phagocytes within the sinusoids can be traced. These phagocytes occur in numerous collections of three to thirty cells each. The individual cells are somewhat variable in size and shape, but all show large vesicular nuclei with chromatin arranged in fine strands and peripheral granules. The cytoplasm is moderate in amount, is finely granular and frequently contains pigment. Occasional cells have included erythrocytes. Eosinophils are numerous throughout the section. Normoblasts appear in considerable numbers, and there are scattered small erythropoietic centers.

Study of bone marrow obtained by sternal aspiration before operation showed approximately 50 per cent of the nucleated forms to be normoblasts. Shortly after operation the proportion was the same. Approximately one year after splenectomy a third aspiration showed approximately 30 per cent normoblasts, with a proportionate increase in neutrophils. No abnormal cells were encountered in any of these studies.

CASE 4.—J. L., a white man aged 62, was admitted to the University of Nebraska Hospital Oct. 21, 1936 and died November 30. The patient had first noticed the onset of undue fatigue one and one-half years before admission to the hospital. This weakness had become progressively more pronounced and was associated with a gradual loss of 37 pounds (17 Kg.) in weight. For about two months he had been aware of vague abdominal distress, which was partially relieved by lying down. He had not been conscious of any abdominal mass until his physician had discovered it some ten days prior to his admission to the hospital. The family history was noncontributory, and the patient's past history was nonessential.

On physical examination the patient appeared to be in a fair state of general nutrition. Except for slight icterus of the scleras, the color was good. The eyes, ears, nose and throat were not remarkable. The heart and lungs were normal for a man of his years. The abdominal examination showed a large mass extending from just under the left costal margin down to and below the umbilicus. The edge of the liver was palpable 2 fingerbreadths below the right costal margin, smooth and not tender. Except for an indirect inguinal hernia on the right side, no other significant physical abnormality was found.

The laboratory examination of the blood showed a hemoglobin content of 11.22 Gm. per hundred cubic centimeters (66 per cent), with a red cell count of 3,210,000 and a white cell count of 2,500. The differential count showed 25 per cent polymorphonuclears, 23 per cent staff forms, 35 per cent lymphocytes, 10 per cent monocytes, 5 per cent atypical lymphocytes and 2 per cent eosinophils. The percentage of reticulocytes was 2.4. The Wassermann reaction of the blood was negative; urinalysis yielded normal results. The fragility of the red cells showed beginning hemolysis at 0.44 per cent and complete hemolysis at 0.30 per cent.

Initial roentgen studies showed a mass in the left upper quadrant of the abdomen, associated with distortion of the renal pelvis, with collapse of the major calices and inferior displacement of the kidney, which was interpreted as a possible neoplasm in the left kidney. Results of further roentgen examination after a barium sulfate enema and production of pneumoperitoneum were interpreted as giving evidence of a possible large retroperitoneal tumor mass, measuring about 8 by 15 by 19 cm., which was displacing the left kidney downward. After the oral administra-

tion of dye, roentgenograms of the gallbladder showed cholelithiasis. Studies of the long bones revealed nothing abnormal; hypertrophic changes were visible in the lumbar portion of the spine.

The anemia was refractory to all forms of treatment during the diagnostic study. On the twenty-sixth day of the patient's stay in the hospital an exploratory laparotomy was done by Dr. C. H. Waters with the patient under spinal anesthesia. The enlarged mass described was found to be due to a tremendously enlarged spleen, and splenectomy was performed. After removal the spleen weighed 2,060 Gm. The liver was slightly enlarged yet of normal appearance and consistency. A thick-walled gallbladder containing stones was encountered. The postoperative course was uneventful until the sixth day, at which time hypostatic pneumonia developed in the lower lobe of the left lung. At this time the blood count showed a hemoglobin content of 12.41 Gm. per hundred cubic centimeters (73 per cent), 4,970,000 erythrocytes and 11,200 leukocytes, with 45 per cent polymorphonuclears, 25 per cent staff forms, 21 per cent lymphocytes, 5 per cent monocytes, 2 per cent basophils and 2 per cent eosinophils. The congestion at the base of the left lung increased, and the patient became gradually weaker; he died on the thirteenth day after operation.

*Pathologic Observations.*—The spleen weighed 2,060 Gm. It was of essentially normal shape. The outer surface was rather deep in color, with numerous lymphoid follicles.

On section there are numerous lymphoid follicles, but relatively few show definite reaction centers. There are numerous small centers of fibrosis through the tissue, usually surrounded by zones of hypertrophied reticular cells with differentiation into free phagocytes. Sinusoids contain large numbers of these phagocytes, but they are usually not arranged in clumps. There is extensive red cell phagocytosis. Eosinophils are present in small numbers. There are scattered normoblasts but no definite erythropoietic foci.

No sternal aspirations were done on this patient.

*Autopsy.*—The site of the recent surgical operation was well healed. The heart was essentially normal. The left lung weighed 1,540 Gm., with almost complete uniform consolidation of the tissue, which on section proved to be typical lobar pneumonia. The splenic vein and artery each contained a thrombus extending through about the distal two thirds of the vessel. The thrombus did not extend into the portal vein or to the celiac axis. The liver was rather large and somewhat pale, with some degree of fatty degeneration evident in the section. The lymph nodes generally showed no abnormalities.

CASE 5.—E. M., a white laborer aged 61, entered the University of Nebraska Hospital for the first time May 7, 1937, complaining of intermittent weakness since 1932. For several months during each of the past five years he had been forced to stop work because of fatigue. About eight months before admission to the hospital a diagnosis of pernicious anemia had been made elsewhere, and oral and intramuscular liver therapy had been instituted. Though considerable improvement was first noted, a severe relapse soon occurred while he was still under intensive liver therapy. Symptoms of marked weakness, dyspnea and palpitation on exertion, dizziness and a lemon yellow pallor had all been slowly progressive in spite of all types of antianemic therapy. He stated that he had had no symptoms of sore tongue, paresthesia or gastrointestinal disturbance. The past and family histories were noncontributory except that a brother had been jaundiced for a short time at the age of 20 years.

On physical examination the patient appeared well nourished. The temperature and the pulse and respiration rates were normal. There was a definite icteric tinge of the skin and scleras, and the mucous membranes were pale. The eyes, ears, nose and throat were normal except for the retinas, examined by Dr. Harold Gifford, which showed many scattered hemorrhages. There was no evidence of redness of the tongue or papillary atrophy. There were a few pea-sized cervical lymph nodes, but lymphadenopathy was not generalized. The lungs were clear, and the heart was not remarkable in rhythm or sounds. There was sclerosis (2 plus) of the radial vessels, and the blood pressure was 112 systolic and 72 diastolic. The spleen was enlarged, being palpable 7.5 cm. below the left costal margin, and was smooth and firm. There were no areas of abdominal tenderness, and no abnormal masses were palpable. The neurologic examination revealed nothing abnormal.

A blood count disclosed a hemoglobin content of 9.69 Gm. per hundred cubic centimeters (57 per cent), 2,860,000 erythrocytes and 3,200 leukocytes, with 30 per cent segmented polymorphonuclears, 31 per cent staff forms, 26 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. A smear of the red cells showed marked achromia with anisocytosis, poikilocytosis with a shift toward the macrocytic side, polychromatophilia and nucleated red cells (5 per hundred white cells). No spherocytes were noted. The mean corpuscular volume was 124 cubic microns; the mean corpuscular hemoglobin content, 32.4 micro-micrograms, and the mean corpuscular hemoglobin concentration, 28 per cent. The percentage of reticulocytes varied from 10.3 to 14.3. The fragility of the red cells to hypotonic solutions of sodium chloride showed beginning hemolysis at 0.32 per cent. The platelets numbered 230,000. The bleeding and clotting times were normal with firm and rapid retraction of the clot. Urinalysis yielded normal results, and the Wassermann reaction of the blood was negative. Analysis of gastric contents showed 13 degrees of free acid and 27 degrees of total acid; examination of the stool did not reveal any blood. The basal metabolic rate was  $-8$  per cent. The blood nonprotein nitrogen was 35 mg. per hundred cubic centimeters. The van den Bergh test showed a direct, delayed, slightly positive reaction, with a quantitative result of 17 mg. per liter. The bromsulphalein test for hepatic function showed 50 per cent retention after five minutes and 10 per cent after thirty minutes. A biopsy of bone marrow taken from the sternum revealed marked hyperplasia of the erythropoietic tissue.

Splenectomy was advised, but the patient refused, and he was dismissed from the hospital with instructions to take weekly intramuscular doses of liver extract and daily doses of reduced iron.

The patient returned to the hospital October 6 with a history of feeling moderately well until six weeks before admission, at which time he first noted vague pain in the upper part of the abdomen associated with frequent attacks of vomiting, increased pallor, deeper jaundice and progressive weakness. The stools were not clay colored, and the pain was not colicky at any time. He requested splenectomy at this time.

The results of physical examination were essentially the same as on the previous admission. The jaundice was definitely more marked and the spleen slightly larger, extending 8 cm. below the left costal margin.

The blood count revealed a hemoglobin content of 4.25 Gm. per hundred cubic centimeters (25 per cent), 1,000,000 erythrocytes and 1,400 leukocytes, with the same differential formula. The fragility of the red cells remained normal, but the percentage of reticulocytes had increased to 37.5, and the result of the quantita-



tive van den Bergh reaction was up to 68 mg. per liter. The icterus index was 35 units. The results of the remaining blood studies were essentially the same as those of the previous examination. Roentgenograms of the gallbladder failed to show any concentration of dye, and no opaque calculi were discerned. The roentgen study of the gastrointestinal tract showed no abnormality.

In an attempt to build up the patient's general physical condition before operation, intravenous injections of dextrose were administered frequently. In addition, transfusions of 500 cc. of whole blood, by the indirect citrate method, were given on two successive days. The hemoglobin content increased to 5.78 Gm. per hundred cubic centimeters (34 per cent), and the red cells to 1,250,000, with 2,600 white cells. Unavoidable circumstances prevented operation being performed at this time. The second day after the second transfusion the patient complained of a recurrence of the vague abdominal pain, which rapidly increased in severity. The jaundice became deeper; the spleen, tender to palpation. What first appeared to be an attack of biliary jaundice was really an acute hemolytic crisis, in which the blood count slowly decreased to 3.4 Gm. of hemoglobin per hundred cubic centimeters (20 per cent), 980,000 red cells and 2,250 white cells. The percentage of reticulocytes was 39; the icterus index increased to 50 units. The stool was highly colored at all times, and the van den Bergh reaction remained indirectly positive. Transfusions were resorted to again and two injections of 500 cc. each were given a day apart, with no apparent reaction. Though the general condition improved somewhat, the blood count decreased to 2.72 Gm. of hemoglobin per hundred cubic centimeters (16 per cent), 510,000 erythrocytes and 2,000 leukocytes, so that emergency splenectomy was performed October 27.

During the first forty-eight hours after operation, the patient's general condition was good and the jaundice noticeably lessened. He was given adequate fluid parenterally and a blood transfusion of 500 cc. immediately after operation and on each of the two succeeding days. On the third day after operation the hemoglobin content had increased to 6.97 Gm. per hundred cubic centimeters (41 per cent), the red cells to 2,210,000 and the white cells to 3,800. The jaundice had almost entirely disappeared. At this time the temperature was 103 F.; the pulse rate, 110 per minute, and the respiratory rate, 35 per minute, associated with increasing abdominal distention. A large amount of serous fluid drained freely from the surgical wound, through which a small tag of omentum had appeared. Signs of free fluid in the abdomen became evident. The patient died the morning of the fifth day after operation, with increasing ascites and coma.

*Pathologic Observations.*—The spleen weighed 1,120 Gm. and measured 22 by 14 by 6 cm. The cut surface showed a rather brownish pulp with fairly distinct lymphoid follicles.

Sections show occasional lymphoid follicles with rather large reaction centers. The pulp is moderately congested. There are numerous eosinophils. There is moderate proliferation of reticular cells, which differentiate to form free phagocytes. These phagocytes occasionally appear in small collections in the sinusoids. Occasional ingestion of red blood cells is encountered. Normoblasts are frequent, and fairly numerous erythropoietic centers are seen.

*Autopsy.*—External examination revealed nothing unusual except the recent surgical incision in the left upper quadrant of the abdomen. Fifty to 100 cc. of fluid was encountered in the peritoneal and pleural cavities. The heart was entirely normal. The right lung showed a few small scattered areas of bronchopneumonic consolidation. The splenic vein was filled with a loosely adherent soft thrombus extending from the operative site to the portal vein and deeply into the liver.

No portion of this thrombus gave the impression of organization. Sections show that it is laminated and of a loose fibrinous character without organization. The gallbladder and the common bile ducts contained numerous small concretions, with no obstruction to the lumen. Sections of lymph nodes in various areas show no abnormalities.

The sternal marrow removed at autopsy shows approximately 50 per cent normoblasts, with no abnormal cells.

#### COMMENT

*Etiology and Classification.*—In attempting properly to evaluate this particular type of anemia, we must admit from the beginning that we have been completely puzzled as to the exact cause and the possible classification. Of the 2 males and 3 females in this series, all were adults whose ages varied from 25 to 62 years. The ages in 4 of the 5 cases ranged from 58 to 62 years. We, as well as others,<sup>2</sup> failed to elicit any history of previous similar attacks in childhood even after the most careful and repeated questioning. Investigation of some of the available relatives did not show evidence of an altered blood picture. The study of each individual case failed to reveal the fundamental cause of the hemolytic mechanism that obviously occurred in each instance. The signs of compensatory hyperactivity of the bone marrow were also a prominent feature. Beyond these facts, however, there was no further clinical evidence of the true basic cause of the disease process. Furthermore, postmortem examination in 3 cases gave no positive tangible clues as to the cause except possibly for the peculiar histiocytic reaction which occurred within the spleen. There was no evidence of the presence of accessory spleens or hemolymph nodes to account for the hemolytic process.

The refractory hemolytic anemia of which we are reporting cases should not be confused with congenital hemolytic jaundice, and the two disorders should be distinguished one from the other. In this respect, difficulty was encountered in attempting to gain help from the literature because of the diverse and often misleading terminology used by different authors. For example, some American writers frequently referred to this type of anemia as the acquired, or adult, type (Hayem-Widal) of hemolytic jaundice<sup>3</sup> or atypical hemolytic anemia.<sup>4</sup> Other authors<sup>5</sup>

2. (a) Davidson, N. S. P.: Macrocytic Hæmolytic Anæmias, *Quart. J. Med.* **1**:543-579 (Oct.) 1932. (b) Lovibond, J. L.: Macrocytic Hæmolytic Anæmia, *Lancet* **2**:1395-1399 (Dec. 21) 1935.

3. (a) Tileston, W.: Hemolytic Jaundice, *Medicine* **1**:355-388 (Aug.) 1922. (b) Rastetter, J. W., and Murphy, F. D.: Acquired Hemolytic Jaundice, *Am. J. Digest. Dis. & Nutrition* **4**:805-810 (Feb.) 1938.

4. Thompson, W. P.: Hemolytic Jaundice: Diagnosis, Behavior and Treatment, *J. A. M. A.* **107**:1776-1781 (Nov. 28) 1936.

5. Cheney, W. C., and Cheney, G.: Chronic Hereditary Hemolytic Jaundice, *Am. J. M. Sc.* **187**:191-212 (Feb.) 1934.

maintained that the acquired and the congenital form of hemolytic jaundice are essentially the same, that they differ only in the age period at which the clinical manifestations become apparent and that the fundamental defect is congenital. It is our opinion that many instances of the so-called acquired type of hemolytic jaundice are in reality congenital, because after a diligent and careful examination of other apparently "well" members of the families of several patients with such disease one of us (J. C. S.) has disclosed a number with a subclinical form of the disorder.<sup>6</sup> Some English authorities deny the existence of the acquired form of hemolytic jaundice,<sup>7</sup> while others designate such disease as macrocytic hemolytic anemia<sup>8</sup> or hemolytic (spherocytic) jaundice in the adult.<sup>6</sup>

Classification of the various hemolytic anemias has been vague and ill defined, chiefly because of the lack of sufficient information. The term hemolytic anemia has proved a useful dumping ground for many obscure diseases of the blood. There has been no clear and accepted definition of what constitutes hemolytic anemia. Pepper<sup>9</sup> has recently called attention to this discouraging state of affairs by asserting, "There are still large gaps in our knowledge of the fundamental process of erythrocytic destruction." He also emphasized the lack of clear separation between the various groups of so-called hemolytic anemias.

Hemolytic anemia appears in many guises and cannot be readily<sup>9</sup> classified as a separate entity. No attempt will be made to classify this group of anemias in this report. In fact, we are not concerned with the hemolytic anemias associated with or secondary to such pathologic conditions as hepatic disease, Hodgkin's disease or leukemia<sup>10</sup> or with those due to sulfanilamide,<sup>11</sup> lead or infections of various types.<sup>12</sup> While in several of the cases reported by Thompson<sup>4</sup> so-called atypical

6. Sharpe, J. C.: Hemolytic Jaundice, *Internat. Clin.* **2**:146-147 (June) 1937.

7. (a) Dawson, B. E.: Hume Lectures on Hæmolytic Icterus, *Brit. M. J.* **1**:921-928 (May 30); 963-966 (June 6) 1931; (b) Indications for and Results of Removal of the Spleen, *ibid.* **2**:699-700 (Oct. 15) 1932. (c) Vaughn, J.: The Anemias, ed. 3, New York, Oxford University Press, 1936, pp. 229-251.

8. (a) Dyke, S. C., and Young, F.: Macrocytic Hæmolytic Anæmia Associated with Increased Red Cell Fragility, *Lancet* **2**:817-821 (Oct. 8) 1938. (b) Kremer, M., and Mason, W. H.: Acholuric Jaundices in the Adult, *ibid.* **2**:849-852 (Oct. 10) 1936. (c) Footnote 2.

9. Pepper, O. H. P.: A Survey of the So-Called Hemolytic Anemias, *Ann. Int. Med.* **12**:796-810 (Dec.) 1938.

10. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia, *Ann. Int. Med.* **12**:1782-1797 (May) 1939.

11. Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, *J. A. M. A.* **109**:1005 (Sept. 25) 1937.

12. Parsons, L. G.: The Hæmolytic Anæmias of Childhood, *Lancet* **2**:1395-1401 (Dec. 17) 1938.

hemolytic anemia was secondary to reticulum cell sarcoma of the spleen, to syphilis or to tuberculosis, there were 9 cases in which no etiologic basis for the hemolytic anemia could be found. Israels and Wilkinson<sup>13</sup> raised the question of whether the cases they reported were instances of true hemolytic jaundice with unusual hyperplastic reaction within the spleen or primary disease of the spleen which had given rise to hemolytic anemia with acholuric jaundice. They expressed the opinion that the evidence supported the former view.

Dameshek and Schwartz<sup>14</sup> recently brought the whole question of the hemolytic syndromes into clearer focus by their experimental and clinical demonstrations of active serum isohemolysin. They expressed the opinion that the various blood pictures of the hemolytic anemias, viz., anemia, spherocytosis, increased fragility and reticulocytosis, are in all probability due to the effects of the varying amount and activity of hemolysins and are modified by the patient's power to react. Their work may well explain the common factor in such supposedly completely unrelated hemolytic syndromes as erythroblastosis foetalis, acute hemolytic anemia of Lederer, acute paroxysmal hemoglobinuria, "pernicious anemia" of pregnancy and up to and including acute or chronic hemolytic (spherocytic) anemia of either the congenital or the acquired type. Such interesting speculation is being further worked out by these authors. Unfortunately, no data were obtained in our studies which either confirm or oppose these views. Josephs,<sup>15</sup> on the contrary, expressed the belief that hemolytic anemia may be due to lack of some substance normally present in plasma, because he has isolated from human and from pig blood plasma a substance which reduces, if it does not completely inhibit, abnormal hemolysis in certain hemolytic anemias.

Davidson and Fullerton,<sup>16</sup> in a study of several cases of such anemia, were unable to offer any explanation for the blood destruction. They also expressed doubt that acute hemolytic anemia of Lederer could be separated from other hemolytic anemias merely because of the claim that blood transfusion apparently produced a cure. Along the same line of

13. Israels, M. C. G., and Wilkinson, J. F.: Hæmolytic (Splenocytic) Jaundice in the Adult, *Quart. J. Med.* **7**:137-151 (Jan.) 1938.

14. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acquired Hemolytic Anemia: A Preliminary Note, *New England J. Med.* **218**: 75-80 (Jan. 13) 1938; Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemia with Particular Reference to the Nature of Spherocytosis and Increased Fragility, *Am. J. M. Sc.* **196**:769-791 (Dec.) 1938.

15. Josephs, H. W.: Studies in Hemolytic Anemia, *Bull. Johns Hopkins Hosp.* **62**:25-76 (Jan.) 1938.

16. Davidson, L. S. P., and Fullerton, H. W.: Some Rare Types of Macrocytic Anæmia, *Quart. J. Med.* **7**:43-85 (Jan.) 1938.

thought, Scott, Robb-Smith and Scowen<sup>17</sup> suggested the possibility that some obscure hemolytic anemias may be formes frustes of the Marchiafava-Micheli syndrome in which the hemolytic anemia is not sufficiently intense to produce hemoglobinuria. Dacie, Israels and Wilkinson<sup>18</sup> have demonstrated autohemolysis in vitro, which was shown to be dependent on the  $p_H$  of the system.

In summary, one can only say that it is impossible to make a coherent story out of the true etiology of hemolytic anemia at present. It remains obscure and in a state of confusion. However, with an increased number of cases of this disease being recognized and studied, an open mind should be maintained with an optimistic attitude toward the solving of the etiologic problems.

*Clinical Manifestations.*—The average duration of symptoms in this group of 5 cases varied from three months to five years. During the course of the disease the clinical picture varied considerably, from chronic (case 3) to subacute (cases 1, 2 and 4). In addition, the alternating periods of remission and relapse were well exemplified in case 5, in which they extended over five years. In no instance, however, was there any indication of a complete and spontaneous disappearance of symptoms after the disease process once became evident.

The clinical symptoms in these cases were those found in any hemolytic type of anemia, that is, weakness, pallor and jaundice. The onset was usually insidious. Loss of weight and a low grade fever were constant features in each case. Vague gastrointestinal disturbances, such as anorexia, epigastric distress, nausea and vomiting, and intermittent diarrhea were frequently present. Dizziness associated with palpitation and dyspnea on exertion was usually a less common complaint. Only 1 patient (case 1) had noted mild paresthesias of the extremities, whereas glossitis was significantly absent in all cases.

On examination all the patients presented various degrees of pallor, icterus and undernutrition. In 3 cases the patients were in a severely critical condition on admission to the hospital. During the observation period, a low grade fever was usually present, with the temperature ranging from 99 to 101 F. For the most part the jaundice was moderately severe, although the intensity would vary from time to time. Because of the hemolytic rather than obstructive character of the icterus, itching of the skin and bradycardia were absent. Splenomegaly was present in each instance. In cases 2 and 4 local pressure symptoms from

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17. Scott, R. B.; Robb-Smith, A. H. T., and Scowen, E. F.: The Marchiafava-Micheli Syndrome of Nocturnal Hæmoglobinuria with Hæmolytic Anæmia, *Quart. J. Med.* 7:95-115 (Jan.) 1938.

18. Dacie, J. V.; Israels, M. C. G., and Wilkinson, J. F.: Paroxysmal Nocturnal Hæmoglobinuria of the Marchiafava Type, *Lancet* 1:479-482 (Feb. 26) 1938.

the enlarged spleen were encountered to such a degree that the possibility of a retroperitoneal or a pararenal tumor mass had to be excluded by roentgen examination of the genitourinary and the gastrointestinal tract before and after the production of a pneumoperitoneum. The liver was clinically interpreted as slightly enlarged in 2 cases, but without frank evidence of hepatic insufficiency or obstruction. In the 2 patients in whom the number of platelets in the blood was reduced (cases 2 and 3), a few mild purpuric spots were found in the skin.

As observed in persons with familial hemolytic jaundice, patients with this type of anemia were also subject to crises of acute blood destruction. During such an episode there was an acute exacerbation of all symptoms and signs, with increased jaundice, pallor, fever and splenomegaly. Epigastric distress occasionally became acute and colicky in nature. The hemoglobin content and the number of red cells decreased rapidly within twenty-four to forty-eight hours. In many instances no direct cause could be elicited for the initiation of these acute attacks. In cases 3 and 5, however, the crises immediately followed the transfusion of whole blood. These unexplained reactions following transfusion have been previously reported more fully, with a note of warning in the consideration of treatment.<sup>19</sup>

*Laboratory Studies.*—The blood in these cases showed a number of interesting and rather characteristic changes. The blood picture varied according to the balance between the mechanism of blood destruction and of compensatory blood formation. The degree of anemia was severe and profound in cases 1, 3 and 5, with the level of erythrocytes just at or under 1,000,000 cells per cubic millimeter. Initial erythrocyte counts in each of the other 2 cases were 3,200,000 and 4,650,000 per cubic millimeter. The erythrocytes were of the macrocytic type in 3 cases, the mean corpuscular volume averaging for the group 118 cubic microns; the mean corpuscular hemoglobin contents 37 micromicrograms, and the mean corpuscular hemoglobin concentration, 31 per cent. These observations are in agreement with those of Kremer and Mason (3 cases)<sup>8b</sup> and Dyke and Young (6 cases).<sup>8a</sup> The hematocrit reading in case 2 showed a hypochromic microcytic type of red cell. The data in case 4 were incomplete in this regard. In all but case 2 reticulocytosis was a striking feature, with the percentage of reticulocytes ranging from 8.4 to 71.6 and averaging 39.2 for the group. In case 2 on repeated examinations before splenectomy the patient had only 0.2 to 1.7 per cent reticulocytes. Studies of the stained blood smear for the presence of spherocytes, so characteristic of familial hemolytic jaundice, failed to reveal their presence in any case. Watson<sup>10</sup> has recently encountered

19. Sharpe, J. C., and Davis, H. H.: Severe Reactions Following Transfusion in Hemolytic Jaundice, *J. A. M. A.* **110**:2053-2056 (June 18) 1938.

increased fragility of the red cells in 2 patients with hepatic disease who had macrocytosis and increased blood destruction. In our cases, however, a number of fragility tests were carried out at different times, without definite or significant abnormality in the results. The tests were carried out before and after splenectomy and on various members of the patients' families who were available. The bleeding and clotting times, as well as the platelet count, showed little change in 3 cases but were somewhat decreased in cases 2 and 3.

Further preoperative hematologic investigation showed in each instance definite and persistent leukopenia, with the white cell count ranging from 1,400 to 4,000 per cubic millimeter. With the exception of case 1, in which there was some slight deviation toward the lymphocytic series, the differential formula was of normal distribution.

The degree of bilirubin present in the serum of these patients was measured by the icterus index, which ranged from 16 to 55 units, with an average of 34.4 units for the group. This hyperbilirubinemia varied from time to time in each case without apparent direct relation either to the degree of anemia or to the size of the spleen. The van den Bergh reaction was positive, usually being of the indirect type. The stools were highly colored with bile, and the reaction for urobilinogen in the urine was positive in dilutions of 1:40 to 1:200 in the 3 cases in which a test was made. Bilirubinemia as a result of obstructive jaundice was not encountered. Tests for hepatic function were performed in 2 cases, with normal results. Fractional analyses of gastric contents gave normal results except for achlorhydria in case 3. In the consideration of the differential diagnosis, the presence of free acid in the gastric contents should help rule out the possibility of pernicious anemia.

In all 5 cases cholecystograms disclosed the presence of biliary calculi. However, as far as we could determine, the cholelithiasis was not the cause of any episodes of colicky pain, obstructive jaundice or clay-colored stools before splenectomy. In case 2 the patient returned to the hospital one year after splenectomy with complaints typical of biliary colic. Subsequent examination of the calculi in 4 cases showed them to be composed chiefly of pigment and calcium salts. Apparently the mechanism for the production of biliary calculi which was present in these cases was similar to that frequently seen in cases of familial hemolytic jaundice.<sup>20</sup> Except for pressure defects from the enlarged spleen, roentgen studies of the gastrointestinal tract showed no gross abnormality which could account for the pathologic process.

*Pathologic Observations.*—There are several features common to the spleens in these 5 cases, as well as some differences. Grossly, all of the

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20. Sharpe, J. C.: Hemolytic Jaundice: Clinical Analysis of Twenty-Eight Cases, *Ann. Int. Med.* **14**:953-959 (Dec.) 1940.

spleens were moderately to markedly enlarged, varying from 550 to 2,000 Gm. in weight. All were of essentially normal shape, that is, showing a general and uniform enlargement. Microscopically, all show reticulum cell hyperplasia as a striking feature, and in some this is the most prominent change. Reticulum cell hyperplasia can be traced through a series of differentiating cells to the formation of free phagocytes. These phagocytes appear in the sinuses in groups or clusters in several of the spleens, although the clumping is not present in all of them. These cells are characterized by rather large vesicular nuclei with prominent sharp chromatin strands and fairly deeply staining cytoplasm. Pigment in moderate amounts has been ingested, and in 4 of the 5 spleens these phagocytes have ingested erythrocytes in greater or smaller numbers. Marked phagocytosis of erythrocytes is evident in only 1 spleen. Normoblasts are present in all of the spleens. In some instances these are present in rather small numbers, while in others they are more numerous and definite erythropoietic foci can be made out. No megaloblastic differentiation is encountered.

Polymorphonuclear and eosinophilic infiltration is present in all of the spleens in varying amounts, and eosinophils in particular are prominent in 3 of the 5 spleens. In only 1 is there evidence of granulopoiesis.

Only in case 3 is there a marked congestion of the pulp suggestive of the change characteristically seen in congenital hemolytic icterus. Three of the 5 spleens show lymphoid follicles rather widely scattered with little evidence of germinal centers. The other two spleens (cases 2 and 5) show well formed reaction centers.

The bone marrow studied was characterized by the marked predominance of erythropoietic activity. This is striking in view of the persistent anemia in this group of cases.

In the 3 cases in which postmortem examinations were done, particular attention was paid to the reticuloendothelial system of various organs and to the character of the lymph nodes. No abnormalities were noted in either tissue.

*Differential Diagnosis.*—The proper evaluation of these cases taxed the diagnostic acumen of the keenest clinician. It was necessary to obtain a detailed history and examination not only of the patient but of all the available relatives. Many various and repeated hematologic determinations were performed to help rule out other dyscrasias of the blood. Biopsy of sternal marrow for the study of bone marrow was necessary. After a careful and detailed period of study and observation, the clinicohematologic syndrome was tentatively placed in the unsatisfactory category of "hemolytic anemia." This was further substantiated



when it became evident that the anemia was apparently refractory to the usual forms of treatment. In the differential diagnosis, one must, of course, consider the following diseases of the blood:

**Familial Hemolytic Jaundice:** Though there is a superficial resemblance between familial hemolytic jaundice and the type of macrocytic hemolytic anemia reported here, there are a number of clinical differences, several definite hematologic dissimilarities and a striking and important difference in the result of treatment. Both diseases have in common the history of weakness accompanied by anemia, jaundice and enlargement of the spleen. Likewise, both syndromes are frequently complicated by secondary cholelithiasis. However, the macrocytic hemolytic anemias tend to occur in an older age group of patients who have not shown any previous clinical manifestations. In addition, there is no sign of the disease in other members of the family. In macrocytic hemolytic anemia the clinical course is usually more severe and of shorter duration than in familial hemolytic jaundice. Furthermore, the jaundice is more intense, the splenomegaly more marked and the hemoclastic crisis of blood destruction more protracted and serious in nature. In a study of the blood the anemia of hemolysis with hyperbilirubinemia and sustained, though varying, reticulocytosis is obvious in both conditions. However, instead of the microspherocytic type of red cell and the increased fragility, so characteristic of hemolytic jaundice, the erythrocytes of this type of hemolytic anemia are definitely macrocytic, with normal or only slightly altered fragility. In contradistinction to the normal leukocyte count or moderate leukocytosis of familial hemolytic jaundice, this group of macrocytic hemolytic anemias presents striking leukopenia. Finally, whereas splenectomy in familial hemolytic jaundice is the treatment of choice, with unquestioned excellent results, removal of the spleen in macrocytic hemolytic anemia is followed by little or only slight improvement in the hemolytic process. This striking difference in treatment between the two disorders will receive more emphasis later. Though one would consider such a differentiation relatively simple, the distinction between these two diseases may give rise to considerable controversy from the standpoint both of diagnosis and of treatment.

**Acute Hemolytic Anemia of Lederer:** This rather rare and acute hemolytic syndrome of unknown origin is usually most common in infants and young adults, rather than in persons of an older age group, such as those in the cases we are reporting. In addition, leukocytosis with myeloid immaturity and mild thrombopenia are rather important differences. Furthermore, a favorable reaction to blood transfusion, causing a dramatic and complete recovery, is a most helpful diagnostic, as well as therapeutic, point.

**Banti's Disease:** This chronic disease, often called splenic anemia, is a syndrome of splenomegaly, progressive anemia and leukopenia associated with a tendency to gastric hemorrhages, hepatic cirrhosis and ascites. Undoubtedly, there is more than one factor responsible for the clinicohematologic changes in Banti's disease. One realizes the anemia under discussion could not be included in this vague category when due consideration is given to the pathologic observations. The absence of fibrosis, the dilatation of the splenic sinuses, the esophageal varices and the changes in the hepatic tissues are striking differences in the two conditions. Furthermore, the anemia of Banti's disease is not hemolytic, and the bone marrow is usually normoblastic.<sup>21</sup>

**Miscellaneous Diseases:** Hodgkin's disease, pernicious anemia, aleukemic leukemia, reticuloendotheliosis, syphilis and malaria must be considered in the differential diagnosis, although distinctive characteristics of each disease make the separation relatively simple.

**Treatment.**—The importance of this group of grave anemias appears to be in the uncertainty of response to the various lines of treatment. In fact, in our cases the disease was characterized by a failure of all available antianemic remedies. It is our opinion that in the future when the basic underlying mechanism of the hemolytic process causing this disease is discovered and, if possible, removed or corrected, the anemia will show prompt improvement. This view is substantiated when we consider the presence of the hyperactive bone marrow and reticulocytosis, which are more than capable of restoring the circulating blood cells to normal, providing the destructive phase of the erythropoietic equilibrium is eliminated. Therefore, until this problem has been solved, one must be contented with a trial of the usual forms of treatment of any severe anemia, with the full realization of their shortcomings and the resulting grave prognosis.

**Liver and Iron Therapies:** We have been unable to see any beneficial effects from oral or parenteral iron or liver therapy, alone or in combination, with or without the vitamin B complex, either before or after splenectomy. This unsatisfactory response has also been the observation of others.<sup>22</sup> Intensive liver therapy has also failed to influence the existing degree of reticulocytosis. Though determinations of the amount of iron in the blood have not been performed in this group of cases, this perhaps should be done in the future. However, one would assume from the evidence at hand that no gross deficiency would be found.

**Transfusion:** Transfusion, as a temporary measure in acute episodes of destruction of the blood and as a routine preoperative procedure, has

21. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1939, pp. 283-284.

22. Dyke and Young.<sup>8a</sup> Kremer and Mason.<sup>8b</sup>

long been advocated by many authorities.<sup>23</sup> Certainly, transfusion is of distinct value in patients jaundiced as a result of biliary and hepatic disease.<sup>24</sup> However, the possible dangerous consequences of transfusions in cases of familial hemolytic jaundice were first pointed out by Lord Dawson<sup>25</sup> in 1931 and later by Hartfall and Stewart,<sup>26</sup> Doan and associates<sup>27</sup> and Lawrence.<sup>28</sup> After a careful analysis, they concluded it was impossible to determine definitely the underlying mechanisms of these transfusion reactions.

The same deleterious effect of transfusion has also been noted in these macrocytic hemolytic anemias. Cases 3 and 5 have served as a basis of a previous report.<sup>19</sup> In addition, Whitby and Britton,<sup>21</sup> as well as Kremer and Mason<sup>8b</sup> have warned of the possible harmful effects of transfusion during a crisis, and Payne<sup>29</sup> has recently reported a fatal reaction. It is our opinion that transfusion is also ineffective as a means of active treatment in the chronic form of this anemia. For example, in case 1 seven transfusions, totaling 3,240 cc. of whole blood, were given before splenectomy and four additional transfusions, amounting to 1,680 cc., after operation, without apparent effect. In other words, after 5 liters of blood was transfused over a period of eight weeks, the level of hemoglobin and red cells remained approximately the same. Lovibond<sup>2b</sup> and Israels and Wilkinson<sup>13</sup> have also had this experience. Since transfusion may at times cause the appearance of alarming symptoms, and even death in an already critically ill patient with macrocytic hemolytic anemia, and since the usual antianemic therapy with iron and/or liver extract is of little or no avail, it seems that one is left with but little to combat the acute episodes of blood destruction.

**Splenectomy:** Removal of the spleen was undertaken in all 5 cases only after the failure of the other forms of antianemic treatment became evident. One would naturally assume that in an anemia of unknown hemolytic character which had failed to respond to ordinary

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23. Hurxthal, L. M.: Hemolytic Jaundice: Consideration of the Diagnosis and Treatment, *S. Clin. North America* **15**:1475-1480 (Dec.) 1935. Tileston.<sup>3a</sup> Cheney and Cheney.<sup>5</sup>

24. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, *J. A. M. A.* **105**:1653-1658 (Nov. 23) 1935.

25. Dawson (footnote 7a and b).

26. Hartfall, S. J., and Stewart, M. J.: Massive Paravertebral Heteropia of Bone Marrow in a Case of Acholuric Jaundice, *J. Path. & Bact.* **37**:455-459 (Nov.) 1933.

27. Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, *Ohio State M. J.* **30**:493-504 (Aug.) 1934.

28. Lawrence, J. S.: Indications for Splenectomy in Medical Practice, *Internat. Clin.* **2**:221-237 (June) 1937.

29. Payne, R. V.: Acute Hemolytic Anemia: Death After Transfusion, *Guy's Hosp. Rep.* **14**:65-71 (Jan.) 1934.

measures removal of a large portion of the destructive process (spleen) in the reticuloendothelial system would cause cessation or retardation of the anemia. In addition, a beneficial effect should be expected when the bone marrow is hyperplastic and there are a great number of young erythrocytes (reticulocytes) in the circulating blood stream attempting to compensate for the blood destruction. On this premise, splenectomy was performed in each of these 5 cases. However, the results were not those we expected. Special detailed blood studies were performed every few minutes during, and at longer intervals after, operation. In no instance was there the dramatic immediate change in the blood followed by a second more gradual and permanent effect, such as takes place in familial hemolytic jaundice. The details of these comparative studies are reported elsewhere.<sup>1</sup> In addition, these patients were poor operative risks and the postoperative complications much too frequent and severe. No such postoperative complications were observed in the 14 patients on whom splenectomy was performed of a group of 31 patients with familial hemolytic jaundice.<sup>20</sup> In our series of patients, 1 (case 5) died on the fifth day after operation of thrombosis of the splenic vein,<sup>30</sup> 1 (case 4) died of postoperative pneumonia one week after splenectomy and 1 (case 2) died of postoperative hemorrhage after a subsequent cholecystectomy, one year after splenectomy. Two patients (cases 3 and 1) are living five and a half and four years, respectively, after splenectomy with moderate, though certainly not complete, improvement. Both these patients continue to have a mild hemolytic type of anemia with leukocytosis but without the acute and severe clinical exacerbations and the crises of blood destruction observed before operation. In our experience we can only state that splenectomy has apparently helped to modify the hemolytic activity, but the clinical and hematologic results are still far from satisfactory.

That splenectomy does not favorably influence the course of macrocytic hemolytic anemia has been shown also by Scott and associates,<sup>17</sup> Lovibond<sup>2b</sup> and Whitby and Britton,<sup>21</sup> Kremer and Mason<sup>8b</sup> concluded that splenectomy is dangerous and unsuccessful in this type of anemia. In 2 of 4 cases reported by Thompson<sup>4</sup> the operation did not result in any change in the activity of the hemolytic process; in the other 2 cases the hemolytic process progressed, and the patients died. Davidson<sup>2a</sup> reported no benefit from splenectomy in 1 case; 1 other patient improved after operation, whereas a third patient improved without removal of the spleen. Israels and Wilkinson<sup>13</sup> reported 4 cases in which splenectomy caused a slow and incomplete recovery. Rastetter and Murphy<sup>3b</sup>

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30. Davis, H. H., and Sharpe, J. C.: Splenic Vein Thrombosis Following Splenectomy, *Surg., Gynec. & Obst.* **67**:678-682 (Nov.) 1938.

removed the spleens of 2 patients; 1 of them improved, but the other had a relapsé and died. Dyke and Young<sup>8a</sup> summarized their experience by stating:

Splenectomy may slightly modify the course of the condition, but it does not cure and its results are in no way comparable to those of familial hemolytic jaundice. Its justification in this condition appears debatable.

#### SUMMARY

Clinical hematologic and pathologic observations in 5 cases of refractory hemolytic anemia in adults are presented.

The hemolytic phase of erythrocytic equilibrium with resultant macrocytic anemia failed to respond to the usual conservative methods of treatment.

In 2 cases transfusion produced dangerous and alarming reactions. Splenectomy in each case failed to modify the course of the disease. Postmortem observations in 3 cases are discussed.

# ACUTE CORONARY THROMBOSIS IN INDUSTRY

## I. DIRECT NONPENETRATING INJURIES, WITH REPORT OF CASES

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The occurrence of acute coronary thrombosis in workers during regular employment has added another facet to the many-sided picture of this clinical entity. The present broad and liberal compensation laws<sup>1</sup> definitely state that if a disease is caused, aggravated or precipitated by an incident arising out of and during the course of employment, then benefits should be paid and the employer assume the costs. A physician must determine whether the medical criteria of the law have been satisfied; namely, was a given incident capable of playing any etiologic role in the resulting disability? This should be a simple matter, but when the criteria are applied to acute coronary heart disease there is so much confusion and biased dogmatism that it is not unusual to find equally competent observers on opposite sides of the same question. This clinical study is presented in the hope of dispelling some of this confusion and of formulating a few broad principles which may aid in justly evaluating the compensability of any given injury, but with the realization that the future may change some of the present concepts.

### MATERIAL

The patients in this study (except in case 5) were workers who sustained industrial accidents arising out of and during the course of employment, followed by acute cardiac conditions for which compensation benefits were claimed. The diagnosis, most often, was acute coronary thrombosis with myocardial infarction, but a better diagnostic term would have been acute traumatic heart disease with myocardial and pericardial damage. These clinical impressions rested on a varying combination of history, physical examination, first medical observations, electrocardiographic and roentgen studies and subsequent clinical course.

The injuries were divided into two large groups, namely, direct nonpenetrating (study I) and indirect injuries (study II) of the heart. The latter group included all those injuries or incidents which could in a remote manner influence the function and structure of the heart, for example, unusual effort, exposure to gases, increased atmospheric pressure or surgical shock.

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1. Workmen's Compensation Law, New York, March 1, 1936, p. 6, paragraph 3, and p. 20, paragraph 2.

Direct nonpenetrating injuries result from an offending force applied directly to the chest without penetrating into its cavities, for instance, a blow; a kick; compression of the chest, or even of the abdomen<sup>2</sup>; impact of a steering wheel; striking the chest against a hard surface; jarring the contents of the chest, as in falling from a height, or perhaps the local application of massive doses of roentgen rays.<sup>3</sup>

Can a direct nonpenetrating chest injury damage the heart? The standard medical<sup>4</sup> and specialized cardiac<sup>5</sup> tests fail to answer this question, and a survey of the current literature revealed numerous reports without agreement on the part of various observers. A few citations will illustrate this diversity of opinion. Bright and Beck<sup>6</sup> collected a large series of cases of fatal heart damage following this type of injury, stressed the importance of early diagnosis and reported a number of cases of nonfatal damage. I<sup>7</sup> recently reported 9 cases of nonfatal injury of the heart, and Warburg's monograph<sup>8</sup> contained some valid examples of this type of heart damage. On the other hand, Stroud<sup>9</sup> commented editorially as follows: "This subject is most important from the standpoint of insurance compensation. I still feel cardiac disease is unusual following anterior

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2. Beck, C. S., and Bright, E. F.: Changes in the Heart and Pericardium Brought About by Compression of the Legs and Abdomen, *J. Thoracic Surg.* **2**:616, 1933.

3. Hartman, F. W.; Bollinger, A.; Doub, H. P., and Smith, F. J.: Heart Lesions Produced by Deep X-Ray: Experimental and Clinical Study, *Tr. Am. Climat. & Clin. A.* **43**:54, 1927. Thibaudeau, A. A., and Mattick, W. L.: Histological Findings in Hearts Which Have Been Exposed to Radiation in the Course of Treatment of Adjacent Organs, *J. Cancer Research* **13**:251, 1929. Werthemann, A.: Experimentelle Röntgenschädigungen des Herzmuskels, *Strahlentherapie* **38**:702, 1930.

4. Cecil, R. L.: Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1937. Osler, W.: Principles and Practice of Medicine, revised by T. McCrae, ed. 11, New York, D. Appleton and Company, 1930. Meakins, J. C.: The Practice of Medicine, St. Louis, C. V. Mosby Company, 1936. Emerson, C. P.: Textbook of Medicine, Philadelphia, J. B. Lippincott Company, 1936. Saville, A., and Warner, E. C.: System of Clinical Medicine, Baltimore, William Wood & Company, 1936. Yater, W. M.: Fundamentals of Internal Medicine, New York, D. Appleton-Century Company, Inc., 1938.

5. Levy, R. F.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936. Levine, S.: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1937. White, P. D.: Heart Disease, New York, The Macmillan Company, 1932. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases, St. Louis, C. V. Mosby Company, 1938.

6. Bright, E. F., and Beck, C. S.: Non-Penetrating Wounds of the Heart, Clinical and Experimental, *Am. Heart J.* **10**:293, 1935.

7. Leinoff, H. D.: Direct Non-Penetrating Injuries of the Heart, *Ann. Int. Med.* **14**:653, 1940.

8. Warburg, E.: Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-Penetrating Traumatic Injuries: A Clinical Study, New York, Oxford University Press, 1938.

9. Stroud, W. D., in Dick, G. F., and others: Year Book of General Medicine, Chicago, The Year Book Publishers, Inc., 1940, p. 699.

chest trauma." These opposing views indicate that physicians are divided over the possibility of heart disease being in any way caused, precipitated or aggravated by direct nonpenetrating injury of the chest.

As a basis for a critical study this material has certain inherent weaknesses, which should be mentioned. In no instance was it possible to duplicate at the bedside the ideal laboratory experiment of making observations before, during and after a given incident. On the contrary, it was necessary to reconstruct events weeks, months and even years later. A skilfully taken history and a thorough examination of all the previous medical reports and observations were important in bridging this gap of time and arriving at a fair clinical conclusion. It is realized that any attempt to relate a given incident to a subsequent pathologic condition is open to the criticism of "because of this, therefore that" type of thinking. This objection is not too valid, since present knowledge is incomplete and the physician's inability to explain a given event does not alter the fact of its occurrence. Besides, cause and effect were often too closely related to be merely coincidental.

#### REPORT OF CASES

CASE 1.—F. D., a 42 year old truck driver, stated that while he was unloading barrels of beer, one of the kegs rolled from the top, struck the front of the chest and threw him to the ground. On arising he was immediately aware of sharp, crushing cardiac pains and seemed unable to breathe. He finished the day's work in spite of symptoms, but about six hours later the pains became severe and crushing in nature, with rapid heart action, marked dyspnea, vomiting and profound weakness. A local physician made the diagnosis of acute coronary thrombosis with myocardial infarction. The past cardiac health had been good.

The patient was seen five days later, at which time he still complained of cardiac pains radiating to both shoulders, difficulty in breathing even while in bed, weakness, vomiting and rapid heart action after any exertion. The retinal arteries were moderately sclerotic. The heart was somewhat enlarged to the left; the sounds were of poor quality, were distant and lacked snap. The first apical sound was less intense than the second, and the second aortic sound was greater than the second pulmonic sound. Normal sinus rhythm was present, with a rate of 90 per minute. The blood pressure was 112 systolic and 80 diastolic. An obvious air hunger and mild shock were present. Serial electrocardiograms indicated acute myocardial damage in that part of the muscle supplied by a branch of the anterior coronary artery, or actually, sinus rhythm, left axis deviation and acute coronary thrombosis of the anterior type. The patient recovered, with marked curtailment of cardiac efficiency.

*Comment.*—Before the accident this man was in good clinical cardiac health, though he had some signs of sclerosis. He sustained a direct nonpenetrating injury of the chest, and immediately afterward symptoms developed, with a complete cardiovascular collapse within six hours.

CASE 2.—H. E., a 37 year old truck driver, stated that while he was removing a quarter of beef weighing about 150 pounds (68 Kg.) from a hook, it slipped out of his grip and struck the front of the chest rather forcibly. In a few moments he felt sharp pains around the heart but not enough to incapacitate him. These pains were continuous and were made worse by exertion, and within forty-eight



hours shortness of breath, weakness, dizziness and vomiting developed. A local physician made the diagnosis of acute coronary thrombosis. The past history was essentially normal, and hard physical work had been previously done without any difficulty.

This patient was seen nineteen days later, at which time the only complaints were occasional cardiac pains, weakness and excessive gas in the stomach. The heart was slightly enlarged to the left (roentgenogram taken at a distance of 6 feet [180 cm.]), the sounds were of poor quality, lacked snap and were distant. The first apical sound was less intense than the second, and the second pulmonic sound was equal to the second aortic sound, with a soft systolic murmur over the pulmonic valve. Normal sinus rhythm was associated with a rate of 80 per

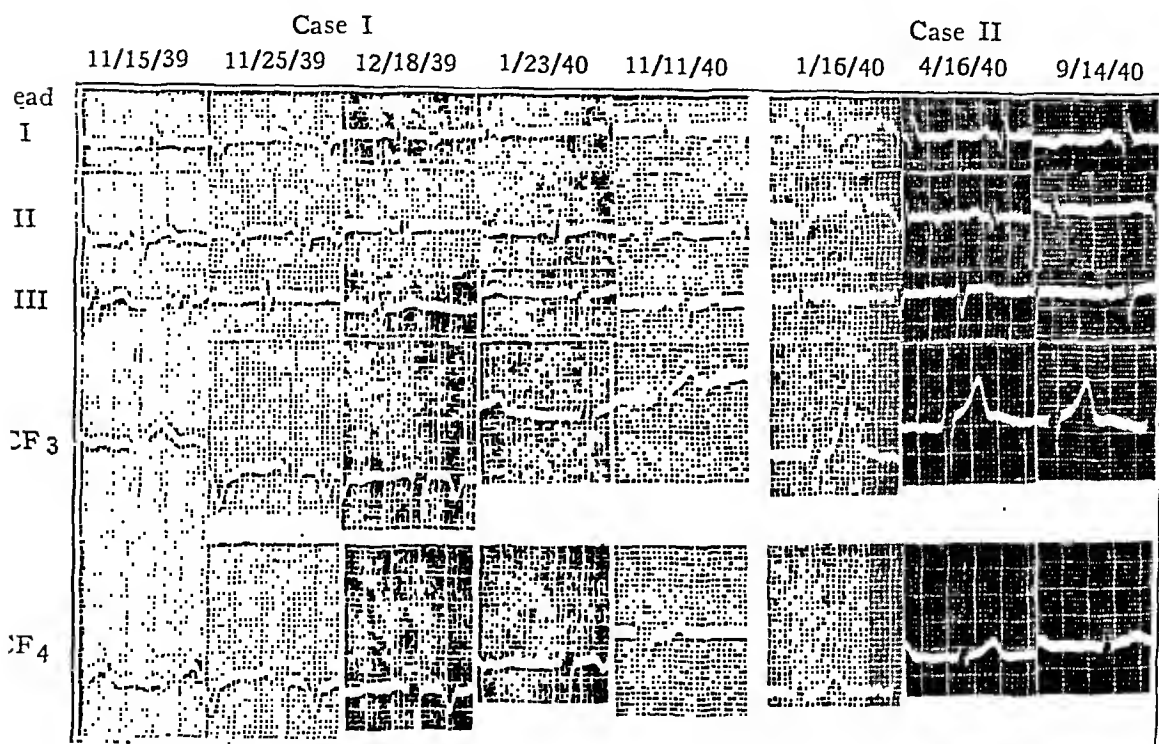


Fig. 1.—Electrocardiograms made in 2 cases of nonpenetrating injury of the chest.

minute. The blood pressure was 98 systolic and 65 diastolic. Serial electrocardiograms showed normal sinus rhythm, left axis deviation and changes indicating myocardial damage and acute coronary occlusion of the anterior type. A better interpretation would have been acute myocardial damage in that part of the heart supplied by a branch of the anterior coronary artery. The first few studies indicated the possibility of pericardial damage. Subsequent examinations indicated an enlargement of the heart, with marked limitation of cardiac function.

*Comment.*—This man was in good clinical health until he sustained a blow to the anterior portion of the chest. Symptoms immediately developed which culminated in a complete cardiac collapse within forty-eight

hours. The original electrocardiograms indicated the possibility of pericardial and myocardial damage.

CASE 3.—H. A., a 38 year old porter, stated that while he was unloading a hand truck, it started to move and threw him off balance; one of the bundles, weighing about 25 pounds (11 Kg.), became dislodged, fell and struck the front of the chest sharply. He felt as though his breath had been knocked out and in a few moments was aware of a burning sensation extending down from the neck to the pit of the stomach. He continued working, but the symptoms became so bad at the end of six hours that medical aid was sought, and a diagnosis of acute coronary occlusion was made. The past cardiac history was normal.

The patient was seen about three and one-half months later, complaining of occasional strange feelings around the heart and an inability to lie on the left side but without any serious curtailment of cardiac function. The eyegrounds showed minimal arteriosclerosis. The heart was slightly enlarged, with some dilatation of the first portion of the aorta; the sounds were of fair quality. The first apical sound was less intense than the second, and the second aortic sound was equal to the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 135 systolic and 90 diastolic. The functional tests showed a good cardiac reserve. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and coronary occlusion of the anterior type.

*Comment.*—This man was in good clinical health until he sustained a trauma to the anterior portion of the chest. Signs and symptoms immediately developed which led to complete collapse within six hours. There were some signs of sclerosis in the eyegrounds and in the aorta.

CASE 4.—J. R., a 45 year old truck driver, stated that in the process of unloading poultry he was struck over the front of the chest by a crate of chickens and immediately became unconscious. He was removed to Morrisania City Hospital, where he remained for a considerable period, complaining of precordial pains, exertional dyspnea and profound weakness. At this institution the diagnosis was acute coronary thrombosis of an unclassified type. The past history was normal.

This man was first seen four years later, in order to evaluate his cardiac status for an operation for hernia. He still complained of exertional dyspnea, inability to lie flat, rapid heart action and effort angina. The retinal arteries were sclerotic. The heart was slightly enlarged; the sounds were of fair quality, and sinus rhythm was present, with a rate of 85 per minute. There was a soft systolic blow at the apex; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. The blood pressure was 120 systolic and 75 diastolic. Roentgen studies showed a moderate dilatation and elongation of the first part of the aorta, with a systolic bulge along the lower half of the left cardiac border. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, ventricular extrasystoles, myocardial damage and possible coronary closure of an unclassified type. There was moderate loss of cardiac efficiency.

*Comment.*—This patient was in good clinical health until he was struck in the chest. He immediately became unconscious, was hospitalized and after his recovery showed persistent signs of insufficiency of the coronary circulation.

CASE 5.—J. M., a 48 year old practicing surgeon, was in an automobile accident, during which the front of the chest was forcibly jammed against the steering wheel. He was dazed, momentarily lost consciousness and then became aware of severe pain over the sternum, rapid heart action and an inability to catch his breath. The pains were made worse by moving, coughing or deep breathing. In addition, there were headaches, dizzy spells and a great deal of body ache. The past history was normal.

This patient was seen thirteen days later, complaining of weakness, cardiac pain, exertional dyspnea and rapid heart action. The left side of the chest was tender on pressure, but roentgen examination failed to show any fractures. The lungs were normal. The heart was normal in size; the sounds were of fair quality. The first apical sound was louder than the second, and the second aortic sound

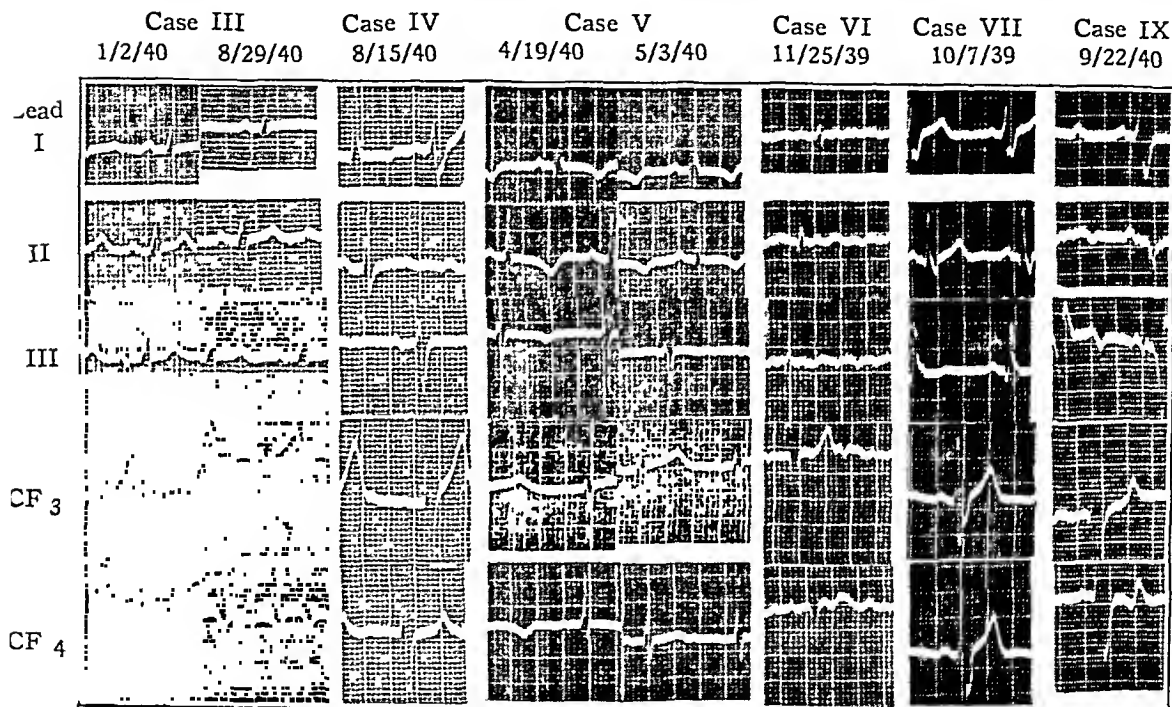


Fig. 2.—Electrocardiograms made in 6 cases of nonpenetrating injury of the chest.

was greater than the second pulmonic sound. The blood pressure was 138 systolic and 80 diastolic. Serial electrocardiograms showed progressive myocardial changes characteristic of anterior coronary closure, sinus rhythm and left axis deviation. The patient made an uneventful recovery and returned to work without any impairment of function.

*Comment.*—Though this case does not represent an industrial accident, it was included because of the nonpenetrating injury of the chest and the heart damage. Immediately after the accident cardiac signs and symptoms developed. The functional recovery was good.

CASE 6.—G. E., a 43 year old janitor, lost his balance and fell down a flight of stairs, striking the head, chest and back. He was somewhat dazed and a few

minutes later became unconscious. He was admitted to the hospital with throbbing pains in the head, marked shortness of breath, rapid heart action and an inability to speak. These symptoms subsided and his ability to speak returned. After his discharge there were persistent shortness of breath, exertional rapid heart action and edema of the ankles, which became so bad that it was necessary for him to reenter the hospital. At this time the diagnosis was rheumatic mitral stenosis, auricular fibrillation and moderate cardiac decompensation. The past history indicated syphilitic infection and an attack of rheumatic fever with involvement of the heart in 1935. The past cardiac functional status was good.

This man was seen ten months after the injury, still complaining of exertional dyspnea, cardiac pains and some swelling of the ankles. The retinal arteries showed some arteriosclerosis. There was a moderate amount of congestion of the bases of both lungs. The heart was enlarged to the left and to the right, and on fluoroscopic examination there was a marked prominence of the right auricle, with a moderate enlargement of the rest of the heart. The heart sounds were of poor quality. Auricular fibrillation was present, with a ventricular rate of 95 per minute and a pulse deficit of 20. The first apical sound was replaced by a systolic murmur. A diastolic murmur was present along the left sternal margin. The second pulmonic sound was louder than the second aortic sound. The liver was enlarged 2 fingerbreadths below the costal margin, and there was pitting edema (1 plus) over both extremities. The blood pressure was 110 systolic and 80 diastolic. The electrocardiographic diagnosis was auricular fibrillation, with a controlled ventricular rate, changes suggestive of myocardial damage and residual signs of anterior coronary occlusion, as indicated by the absence of the R wave in lead IV. The patient remained under observation, and during the latter part of 1940 he had a cerebral accident and died.

The report of the postmortem examination was as follows: "The heart is enlarged both to the right and to the left. The right auricle is larger than normal. The tricuspid valve is normal. The left ventricle is enlarged, and the endocardium is grayish white and firm; it shows evidence of fibrosis; the pulmonic valve is normal. There is marked arteriosclerosis along the course of the pulmonary artery at its bifurcation. There is no evidence of pulmonary embolism. The mitral valve looks like a funnel and admits the tip of one finger only. There is a large, fresh, friable vegetation along the line of closure. The mitral valve is thickened and calcified in some areas. The chordae tendineae are thickened and shortened. The papillary muscles seem to be implanted on the valve. The large thrombus formation just noted is present in the dilated left auricle. An aneurysmal dilatation about the size of a quarter is present at the apex, with the myocardium markedly thinned out on the left side. White strands stand out prominently on the endocardial surface of the left ventricle. The aortic valve is normal in size; the cusps are thin and delicate, and the commissures are not widened. There are isolated arteriosclerotic plaques along the course of the aorta. The ostiums of the coronary arteries are patent. The coronary vessels are sclerotic and the lumens narrowed. There is no evidence of occlusion, however."

*Comment.*—According to his history, this patient was in good clinical health aside from a quiescent rheumatic infection of the mitral valve. He was able to do regular hard work without any difficulty. After the injury to the chest he became unconscious and from then on presented cardiac symptoms. In addition, there was a transient cerebral involve-

ment. The diagnosis was mitral stenosis, auricular fibrillation and possible traumatic injury to that part of the heart supplied by a branch of the anterior coronary artery. There were an underlying rheumatic infection, sclerosis of the coronary arteries and possibly syphilis, all confirmed at autopsy. The small aneurysmal dilatation of the left ventricle located near the apex, but not associated with any coronary closure, in retrospect may have been the site of a contusion and subsequent scarring. This is speculative, but if all the facts are kept in mind it does not seem an unreasonable possibility.

CASE 7.—M. D., a 52 year old foreman of a milk-loading depot, lost his balance and fell, striking the front of the chest sharply against the conveyor and a case of milk. He immediately felt weak and dizzy and was conscious of rapid heart action. He rested a short while but noticed that any effort brought on symptoms which became so bad three days later that he applied for medical aid. Before the injury he was in good physical health and had been doing hard physical work on one job for twelve years without any loss of time.

This man was examined two and one-half months later, still complaining of exertional dyspnea, marked weakness and dizziness. He appeared much older than his stated age. The retinal arteries were moderately sclerotic. The heart was normal in size; the sounds were distant, muffled and of poor quality over the base. Normal sinus rhythm was present, with a rate of 80 per minute. The first apical sound was equal to the second, and the second pulmonic sound was greater than the second aortic sound. The blood pressure was 108 systolic and 88 diastolic, and after a functional test the pulse rate remained elevated. Roentgen examination revealed diminished movements of the left lower border of the heart. An electrocardiogram revealed a normal sinus rhythm, ventricular extrasystoles, right axis deviation, changes indicative of myocardial damage and possibly residual signs of an atypical coronary closure.

*Comment.*—This patient was in good clinical health until the chest was traumatized. Immediately, he displayed signs and symptoms of insufficiency of the coronary circulation which were progressive and became so bad in three days that work was discontinued. Serial electrocardiograms failed to reveal the progressive changes usually associated with fresh myocardial lesions. If the past history is true, then this injury immediately changed the clinical status of this man.

CASE 8.—A. J., a 64 year old druggist, was struck by an automobile while he was crossing the street. He was admitted to the Flower and Fifth Avenue Hospitals in shock, unconscious and cyanotic, with a slow pulse. Roentgenograms showed fractures of the fourth, fifth, sixth, seventh and eighth ribs on the left side; multiple fractures of the pelvis, and a left hemothorax. He gradually recovered from the shock but continued to complain of severe pain in the chest and other parts of the body. Five days later, after a bowel movement, he suddenly became dyspneic and cyanotic and exhibited all the signs of shock and collapse. The past history was normal.

This man was seen seven days after the accident and presented essentially the same picture as just described. The heart was slightly enlarged, and the

sounds were of poor quality. The first apical sound was less intense than the second and the second pulmonic sound was greater than the second aortic sound. Normal sinus rhythm was present, with a rate of 65 per minute, and the blood pressure was 155 systolic and 55 diastolic. There was some fluid in the left pleural cavity. Serial electrocardiograms revealed changes suggestive of an acute type of heart damage. He made an uneventful recovery, but the fractures precluded any clinical evaluation of cardiac function.

*Comment.*—This patient was in good clinical health until he sustained a rather severe type of injury. It is interesting to note that on admission, in spite of the shock, the patient's pulse was rather slow. This phenomenon has been noted in some experimental animals.<sup>10</sup> The care of the fractures dominated the clinical picture, and it was not until the

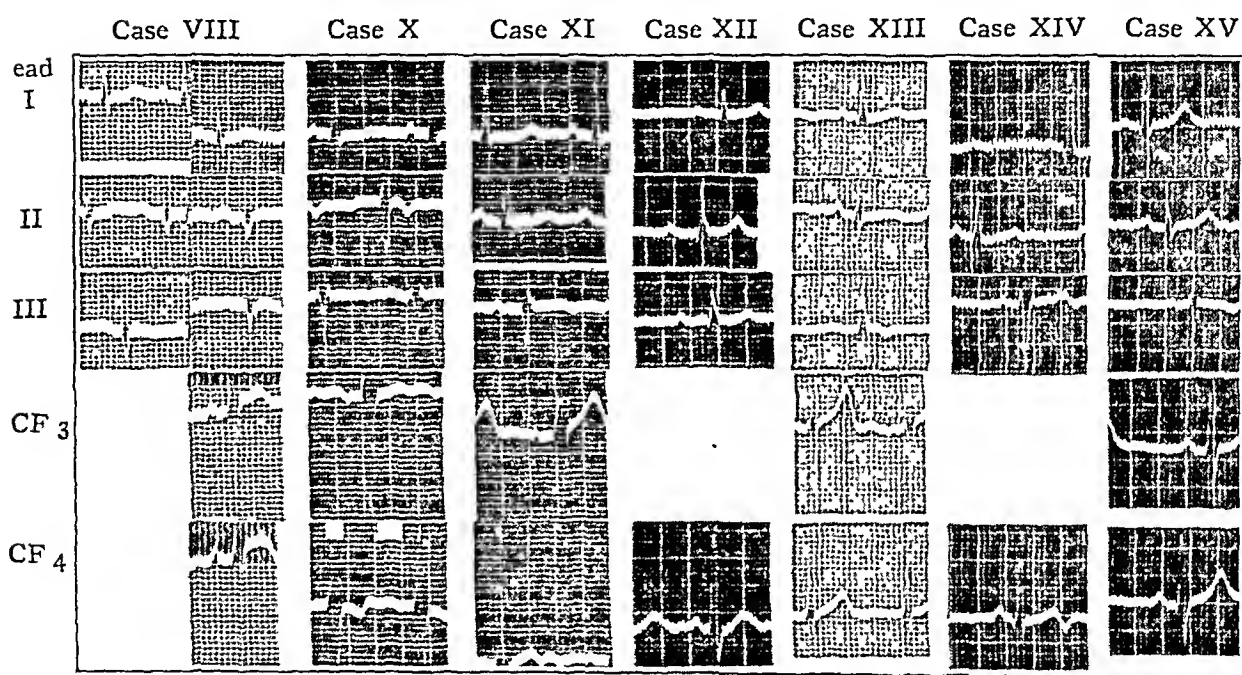


Fig. 3.—Electrocardiograms made in 7 cases of nonpenetrating injury of the chest.

patient had a complete cardiac collapse that investigation revealed signs of acute heart damage. This acute condition may have represented a pulmonary embolus or a spontaneous coronary occlusion, but subsequently the classic picture of either of these two conditions did not develop. The extensive type of chest injury suggested a traumatic factor in the cardiac picture.

CASE 9.—P. K., a 62 year old porter, stated that while backing a load of wood, he lost his balance and fell, striking the left side of the chest sharply against the handle of the truck. In addition, he hurt his hip, leg and scrotum. He immediately felt sharp pains around the heart and was unable to breathe properly. He was given

10. Moritz, A. R., and Atkins, J. P.: Cardiac Contusions: An Experimental and Physiologic Study, Arch. Path. 25:445 (April) 1938.

local treatment, but the symptoms, particularly the shortness of breath, became so bad that he was put to bed for six weeks. He then returned to do light work, but the dyspnea, precordial pains and weakness persisted. These symptoms were progressive, and the patient finally collapsed with severe cardiac pains, vomiting and shortness of breath about two months later. Since then he has remained at home and has been unable to work because of these symptoms. The roentgenogram showed a fracture of the ribs on the left side. In addition, there was a traumatic hydrocele of the right testicle. Before the accident he had been in good health and was able to do hard physical work, without any limitations.

This man was examined about three years after the original accident and still complained of exertional dyspnea, cardiac pains and swelling of the right testicle. The retinal arteries showed moderate arteriosclerosis. There was a hydrocele of the right testicle. The heart was enlarged, and the aorta was somewhat dilated. The heart sounds were of fair quality but lacked snap; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. There was a short systolic murmur at the apex. The blood pressure was 122 systolic and 70 diastolic, and a few rales were present over the bases of both lungs. A simple bending exercise produced air hunger. The electrocardiogram revealed a normal sinus rhythm, left axis deviation, changes indicative of myocardial damage and possible residual signs of posterior coronary thrombosis. There was rather extensive limitation of cardiac efficiency.

*Comment.*—This patient was in good clinical health until he sustained a rather severe direct nonpenetrating injury of the chest. He immediately displayed signs and symptoms which persisted and finally culminated in complete cardiac collapse.

CASE 10.—C. K., a 54 year old truck driver, stated that while he was waiting for a red traffic light to change, the rear of his truck was hit by another car, and his chest was violently thrown forward against the steering wheel. At the same moment his right foot, which was on the foot brake, was violently pushed upward and caused a compression of the leg on the abdomen. He was immediately aware of severe pains in the abdomen, heart and head. These symptoms and exertional dyspnea persisted and gradually became worse. Two weeks later, while carrying a heavy object up three flights of stairs, he suddenly collapsed with severe cardiac pain, nausea, vomiting, weakness and dyspnea. He was put to bed and presented the clinical picture of a complete cardiac breakdown, with edema of the ankles. The past history indicated no difficulty in doing hard work for the preceding twelve years.

This man was seen about a year and a half later, at which time he complained of precordial pain radiating to the shoulder, dyspnea, dizzy spells, weakness and a lump in the stomach. The eyegrounds showed arteriosclerosis (1 plus). The chest was barrel shaped. The heart was moderately enlarged. The aorta was somewhat dilated, and the left cardiac margin showed diminished movements. The heart sounds were of poor quality, were muffled and lacked snap. The first apical sound was less intense than the second, and the second aortic sound was equal to the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 118 systolic and 90 diastolic. The liver was enlarged and tender. After a simple bending exercise the patient showed obvious air hunger. The electrocardiogram revealed a normal sinus rhythm, left



axis deviation, changes indicative of myocardial damage, coronary occlusion of the posterior type and changes due to digitalis therapy. There was marked curtailment of cardiac function.

*Comment.*—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Immediately signs and symptoms developed which persisted and ended in the subsequent collapse.

CASE 11.—J. M. R., a 55 year old salesman, stated that the car he was driving skidded and struck an elevator pillar. His chest was forcibly crushed against the steering wheel. He was immediately aware of precordial pains, weakness and some difficulty in breathing. After being allowed out of bed he noticed excessive shortness of breath and exertional distress. Before the injury there had been similar symptoms but evidently not severe enough to interfere with his work.

This patient was seen about four months after the injury, with the same complaints. The eyegrounds showed some arteriosclerosis. The aorta was somewhat dilated and elongated. The heart was moderately enlarged to the left. The heart sounds were of poor quality and lacked the characteristic normal snap. The first apical sound was equal to the second, and the second pulmonic sound was equal to the second aortic sound. The blood pressure was 168 systolic and 104 diastolic. The electrocardiographic diagnosis was normal sinus rhythm, changes indicative of myocardial damage, left axis deviation and possible residual signs of posterior coronary occlusion.

*Comment.*—There was some disability before the accident due to the coronary sclerosis but not enough to keep the patient from working. After a direct nonpenetrating injury of the chest signs and symptoms developed which ultimately led to complete disability.

CASE 12.—L. K., a 60 year old plumber, fell from the top of a ladder and struck his chest rather sharply against the ground. He immediately felt weak, had a desire to vomit and experienced difficulty in breathing. He rested for a while and then attempted to work. In addition to the symptoms just mentioned, he noticed a pressing sensation in the pit of the stomach and under the breast bone. These symptoms continued, gradually becoming worse, and about a month later, while carrying his bag of tools, weighing 65 to 75 pounds (30 to 34 Kg.) up four flights of stairs, he collapsed with severe pains in the chest, weakness and dizziness. The past history was normal.

This man was first seen about six months after the accident, with essentially the same complaints. The heart was slightly enlarged; the heart sounds were of poor quality; the first apical sound was equal to the second, and the second aortic sound was equal to the second pulmonic sound. The blood pressure was 130 systolic and 85 diastolic. The electrocardiogram revealed normal sinus rhythm, first degree heart block and changes indicative of myocardial damage.

*Comment.*—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Cardiac symptoms then developed which were progressive and culminated in complete collapse.



CASE 13.—A. K., a 46 year old manager of a bakery shop, slipped and fell down a flight of stairs, striking the lower portion of his chest and back on the left side. He immediately felt pain in the chest, rapid heart action, weakness and dizziness. These symptoms persisted, and a few hours later, the patient began to vomit and the pains returned in a severe form. A diagnosis of coronary occlusion was made. Before the accident the patient had been doing hard physical work without any difficulty.

This man was first seen four months later, complaining of exertional pain and dyspnea, rapid heart action and spells of dizziness and weakness. The eyegrounds showed moderate arteriosclerosis. The heart was moderately enlarged, and the sounds were of a fair quality. The first apical sound was equal to the second, and the second pulmonic sound was equal to the second aortic sound. There was a systolic murmur at the apex. The blood pressure was 152 systolic and 116 diastolic. The electrocardiogram showed normal sinus rhythm, left axis deviation, changes suggestive of myocardial damage and residual signs of coronary occlusion of the nonclassified type. There was moderate curtailment of cardiac efficiency.

*Comment.*—This patient was in good clinical health until he sustained a nonpenetrating injury of the chest. Immediately he exhibited signs and symptoms of acute insufficiency of the coronary artery circulation.

CASE 14.—A. K., a 65 year old janitress, tripped over a floor mop and fell, striking the head, face and front of the chest. She immediately felt sharp pain in the chest and seemed unable to breathe. Her subsequent complaints were exertional dyspnea and cardiac pains, weakness and edema of the ankles. Though she stated her past history was normal, testimony indicated she had preexistent angina pectoris; however, there was no doubt about the accident.

This woman was seen four months later with the same complaints. The eyegrounds were mildly sclerotic. The heart was enlarged. The heart sounds were of fair quality, though lacking in snap. The first apical sound was louder than the second, and the second aortic sound was equal to the second pulmonic sound. There was a soft systolic murmur at the apex. The blood pressure was 130 systolic and 70 diastolic. There was slight congestion at the bases of both lungs. After a simple bending exercise there was obvious air hunger. The electrocardiogram showed left axis deviation, normal sinus rhythm, changes indicative of myocardial damage and residual signs of posterior coronary occlusion.

*Comment.*—This case illustrates the importance of the past history. The patient evidently had antecedent angina pectoris with clinical symptoms. Without an accurate history the whole cardiac picture would have been attributed to the fall, whereas this injury only aggravated her previous condition.

CASE 15.—A. W., a 61 year old painter, fell from the top of a ladder, a distance of 6 feet (183 cm.) and struck the chest and body and fractured the right os calcis. He immediately felt pains in the foot and over the heart. While in bed, he complained of cardiac pains, dizzy spells and weakness. When he resumed his activities, he noted a persistent shortness of breath which had not been present

before. On returning from the first visit to his physician, it was necessary for him to climb four flights of stairs on crutches. This started a great deal of cardiac pain, dyspnea, dizziness and weakness, and a diagnosis of coronary occlusion was made. The past history indicated ability to do hard physical work without any difficulty.

This patient was first seen three months after the accident, with essentially the same complaints. The retinal arteries showed some sclerosis. The heart was slightly enlarged; the lower left margin showed decreased movements, and the aorta was somewhat dilated. The heart sounds were of poor quality; the first apical sound was louder than the second, and the second aortic sound was greater than the second pulmonic sound. Normal sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 112 systolic and 80 diastolic. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and possible residual signs of posterior coronary occlusion. There was marked curtailment of cardiac efficiency.

*Comment.*—This patient was in good clinical health until he sustained a direct nonpenetrating injury of the chest. Cardiac symptoms then developed, and after the unusual exertion of climbing four flights of steps on crutches for the first time, he sustained an acute coronary occlusion. In this patient there is a combination of a direct and an indirect trauma. It is possible that the former produced little damage and that the latter was mainly responsible for the clinical picture which followed.

CASE 16.—M. G., a 48 year old store clerk, stated that he slipped and fell on a flight of stairs, striking the front of the chest rather sharply. The injured part felt bruised, but no shortness of breath, weakness, etc., were noted at the time. He continued working for five hours without any difficulty. That same night he was awakened from a sound sleep (twelve to fourteen hours after the injury) by sharp, squeezing precordial pains. He was kept in bed the following day; the symptoms subsided, and he then returned to work. This time he engaged in his regular occupation for twelve hours without noticing any unusual symptoms, but that same night after having fallen asleep he was awakened by severe substernal pains, nausea, vomiting, weakness, rapid heart action and dyspnea. A diagnosis of acute coronary occlusion was made. He gave a past history which did not include any previous cardiac complaints and stated that he had been able to do hard work without any difficulty. However, his physician gave a history of a similar attack of angina, vomiting, weakness and change in blood pressure occurring about eight months before the present illness.

This patient was seen six days after the accident and complained of the same symptoms just noted. The eye grounds were sclerotic. The heart was boot shaped and moderately enlarged to the left; the aorta was dilated and elongated. Normal sinus rhythm was present, with a rate of 75 per minute. The sounds were of poor quality and muffled; the first apical sound was less intense than the second, and the second pulmonic sound was greater than the second aortic sound. The blood pressure was 120 systolic and 80 diastolic (at the time of the first attack it had been 230 systolic and 120 diastolic). During this examination, rather strong pressure over the precordium with the stethoscope failed to elicit any complaints

of pain and no external signs of injury were present. The electrocardiographic diagnosis was normal sinus rhythm, left axis deviation, myocardial damage and acute coronary thrombosis of a posterior type.

*Comment.*—This case was particularly instructive. If the physician's account of the patient's history is accepted, during the first night after injury the patient had a severe attack of angina, from which he recovered, and two nights later a coronary occlusion developed, both on the basis of hypertensive arteriosclerotic heart disease. With this history in mind one may doubt that the patient even had a fall, inasmuch as this was not reported to any one at the time of its occurrence and may have been a thought in retrospect.

On the other hand, if the patient's history is accepted, it will be noted that no cardiac symptoms appeared until many hours after the injury. The complete breakdown occurred forty-eight hours later while the patient was asleep and after he had worked twelve hours without any difficulty. In the experimental reports signs and symptoms appeared and persisted after the trauma. In the presence of a hemopericardium it is possible that some symptoms would appear, but the total breakdown would be delayed. A contusion of the myocardium would produce functional disturbances at once and not after a delay of forty-eight hours or longer. In this case the injury, if it did occur, was only incidental.

CASE 17.—R. F., a 49 year old laborer, fell from an 8 foot (244 cm.) ladder, striking his head, the lower part of the back and the chest. One of the lumbar vertebrae was fractured, and a cast was applied. At this time and subsequently he complained of local pains. Eight months later he suddenly fainted and remained unconscious for five hours. Since then there have been shortness of breath, swelling of the ankles, rapid heart action, precordial pain and weakness. The past history was essentially normal.

This man was seen about nine months after the accident, complaining of the symptoms just mentioned. The heart was enlarged. The sounds were of poor quality and seemed somewhat distant. Auricular fibrillation was present but without any murmurs. The ventricular rate was 90 per minute, with a pulse deficit of 30. The blood pressure was 110 systolic and 80 diastolic. The electrocardiographic diagnosis was auricular fibrillation, myocardial damage and changes due to digitalis therapy, with a slow ventricular rate.

*Comment.*—This case was included because a claim was made for the cardiac disability on a traumatic basis. The patient evidently suffered an acute coronary occlusion about eight months after the accident. In view of clinical and experimental experience this could in no way have been related to the original injury because of the time interval. Here again an accurate history was important.

CASE 18.—S. B., a 33 year old florist, slipped on a wet floor and fell, striking the front of the chest sharply against the edge of an ice box. He was immediately

aware of sharp cardiac pains, difficulty in breathing and extreme weakness. The left leg was bruised against a pail on the floor. Within six hours the thoracic pains became so bad that he was put to bed by his physician. At this time there were signs of external injuries, such as discolorations and small abrasions. After several weeks the symptoms subsided. The past history was normal.

He was seen three weeks later, complaining of slight cardiac pains. The heart was normal in size, position and movements. The heart sounds were of good quality; the blood pressure was 110 systolic and 70 diastolic, and the lower end of the sternum was tender on pressure. The electrocardiographic diagnosis was

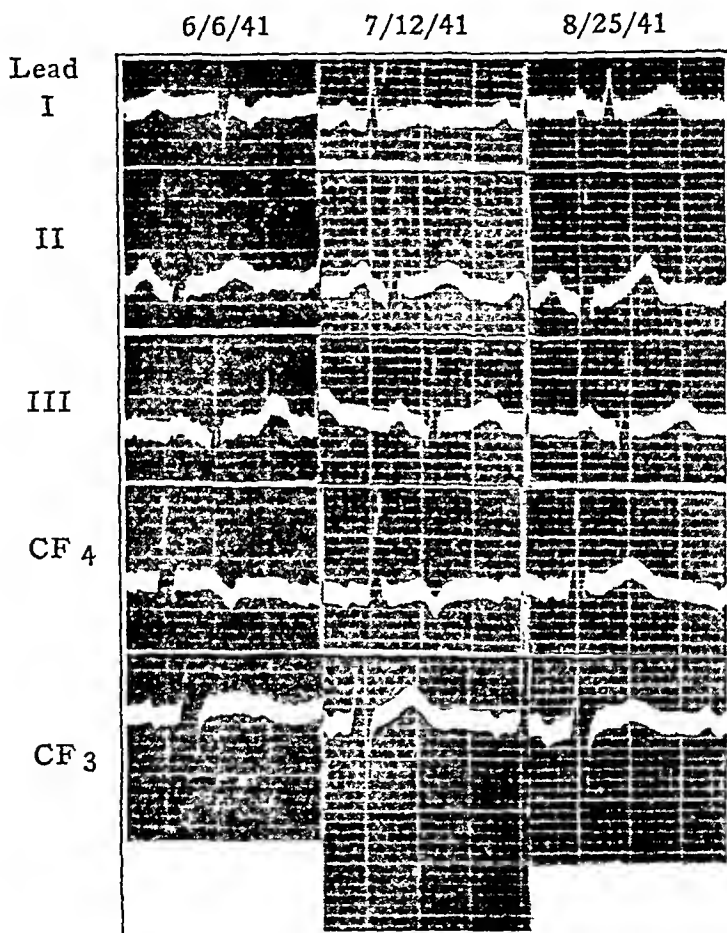


Fig. 4.—Electrocardiograms made in a case of nonpenetrating injury of the chest.

normal sinus rhythm, absence of axis deviation and acute myocardial damage in an area supplied by the anterior coronary artery. This was confirmed by serial tracings.

*Comment.*—This man exhibited acute electrocardiographic changes after a chest injury. This case illustrates the importance of electrocardiographic study in all instances of trauma to the chest. The functional recovery was complete several months later. This case is not included in the section headed “Comment.”

## COMMENT

*Incidence.*—No accurate statistics are available as to the frequency of nonfatal cardiac damage after nonpenetrating injuries of the chest. The numerous current reports indicate that this is not a clinical rarity and that the condition will probably be recognized more often in the future.

*Sex.*—All except 1 of the patients were males. This predominance is probably due to the more strenuous physical tasks performed by men in industry.

*Age.*—Only 2 patients were under 40 years of age, and the rest were evenly distributed among the fourth, the fifth and the sixth decade. Young and old persons alike are subject to this type of injury, but in the latter an underlying quiescent process may complicate the resulting picture.

*Occupation.*—The actual nature of the work was not as important as the kind of accident. In the whole group of cases the injuries were evenly divided between the light and the heavy industries.

*Trauma.*—The injury was considered an important etiologic factor in the first 15 cases and only as incidental in the last 2 (cases 16 and 17). The offending force varied as to quality, quantity and point of application.

The chest was injured by heavy objects in 34 per cent of cases (1, 2, 3, 4 and 9); by striking a hard surface, as in falling, in 40 per cent of cases (6, 7, 12, 13, 14 and 15), and by automobile accidents in the remaining 26 per cent of cases (5, 8, 10 and 11). In this last group, the injury was caused by impact with a steering wheel in 3 cases and in 1 case the patient was struck by a car.

The anterior part of the thorax on the left side was the point of application in 10 cases and the left side and the back of the thorax in 5 cases. These figures are the same as those in current reports in the literature.

A rough division indicated that the offending force was moderate in 9 cases, rather severe in 5 cases and mild in 1 case.

External signs of injury were present in 60 per cent of cases (2, 4, 5, 6, 7, 8, 9, 10 and 11) and absent in 40 per cent of cases (1, 3, 12, 13, 14 and 15). These figures are in accord with the present consensus that the absence of such signs does not preclude cardiac damage.

*Mechanism of Trauma.*—Penetrating injuries of the heart were recognized and considered invariably fatal for many centuries, until an increasing number of survivals evolved a syndrome which could be recognized and treated successfully. A nonpenetrating lesion does not enjoy the same clearcut recognition, and even its very existence is doubted.

Clinical reports,<sup>11</sup> laboratory data<sup>12</sup> and the files of the medical examiner of any large city offer ample proof that fatal and nonfatal cardiac damage may result after this type of injury. Postmortem examination of persons killed in automobile accidents often reveals incidental acute cardiac lesions which were not responsible for death.<sup>13</sup> In many survival experiments the animals used as subjects showed objective traumatic lesions. In case 6 autopsy revealed a lesion of the left ventricle, the nature of which suggested a traumatic origin.

During this type of injury the heart may be violently thrown against the bony parts; actually be compressed; be torn from its attachments; have its chambers burst open; be jarred, as in falling; have the blood forced back into the ventricles or prevented from leaving by compression, thus increasing intracardiac pressure, or be bruised by fractured bones pressing against its surface. In any given case one or all of these factors may operate.

The resulting damage is a combination of structural and functional changes, which do not necessarily parallel each other. In the animal laboratory death was not always associated with extensive lesions, whereas in the survival experiments moderate and even extensive lesions were apparent, with little dysfunction. The most common findings were single or multiple lacerations, contusions, hemorrhages and ruptures, of one or all of the layers of the heart.<sup>10</sup> The subsequent healing took place by fibrosis and scarring. Occasionally acute dilatation was seen. The role of reflex coronary spasm was important in explaining the diffuse and disseminated pathologic and physiologic changes which sometimes followed a single blow. Moritz and Atkins stressed the similarity of the changes occurring after experimental trauma and after coronary occlusion.

In the laboratory numerous types of arrhythmia followed artificial trauma. In this group of cases fibrillation developed only in case 6.

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11. (a) White, P. D., and Glendy, R. E., in Brahdly, L., and Kahn, S.: *Trauma and Disease*, Philadelphia, Lea & Febiger, 1937, p. 59. (b) Bright and Beck.<sup>6</sup> (c) Warburg.<sup>8</sup>

12. Schlomka, G.: Experimentelle Untersuchungen über den Einfluss stumpfer Brustkorbtraumen auf das Herz, *Ztschr. f. d. ges. exper. Med.* **93**:751, 1934. Kulbs, F.: Experimentelle Untersuchungen über Hertz und Trauma, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **19**:678, 1939. Kulbs, F., and Strauss, L. H.: Herz und Trauma; Weitere experimentelle Untersuchungen, *Klin. Wchnschr.* **11**:1572, 1932. Kissane, R.; Fidler, R. S., and Korns, R. A.: Electrocardiographic Changes Following External Chest Injury to Dogs, *Ann. Int. Med.* **2**:907, 1937. Bright and Beck.<sup>6</sup> Moritz and Atkins.<sup>10</sup>

13. Barber, H.: Contusion of the Myocardium, *Brit. M. J.* **2**:520, 1940. Leinoff.<sup>7</sup>

This change must be accepted with reservations, since in this case there was antecedent mitral stenosis. In case 8 there was an immediate slow pulse, in spite of all the outward signs of shock.

Those animals which died after experimental trauma invariably showed a marked curtailment of function immediately after the application of the offending force. This same change was observed to a greater or less degree at the bedside.

*Clinical Considerations.*—In this type of chest injury the heart may or may not be damaged. Minor lesions probably escape clinical detection because this condition is not suspected and proper diagnostic measures, such as serial electrocardiograms, are not taken.

The composite picture in this study closely resembled acute coronary occlusion with infarction. This is not surprising when it is realized that in both conditions the findings depend on acute myocardial changes. Signs and symptoms usually developed after the injury, just as after experimental trauma. The most common symptoms were pain, respiratory difficulty, rapid heart action, dizziness, unconsciousness and weakness. In case 5 these symptoms gradually subsided, but in most of the other cases they persisted, gradually became worse and usually ended in the clinical picture of shock and cardiovascular collapse. The objective findings were poor heart sounds; disturbances of rate and rhythm; normal blood pressure; the presence of a systolic murmur, perhaps due to a mild dilatation of the left ventricle, and electrocardiographic changes. It is possible that many of the changes observed in animals would be noted in patients if this condition was recognized early enough. These signs are dilatation, a falling arterial and a rising venous pressure, tick-tick rhythm, poor heart sounds, disturbances of conduction and rhythm, ventricular fibrillation, etc.<sup>6</sup> The acute picture may be further complicated by lacerations of the heart and its coverings, a hemopericardium and underlying quiescent processes, such as arteriosclerosis. The last-named factor was present to some degree in practically all cases.

After the acute phase the signs and symptoms depend on the amount of residual damage, the degree of healing and the efficiency of the reestablished circulation. Thus it can be seen that the picture is essentially the same as that in coronary occlusion and can be differentiated only by means of the history (cases 16 and 17). In cases 11 and 14 the injury probably produced only a symptomatic aggravation of a preexisting disease.

The history, which is a word picture of events before, during and after a given incident, is the most important single factor in any con-

sideration of trauma and subsequent disability. The objective changes caused by an injury may be the same as ones caused by other factors, and only the history will enable an observer to formulate an opinion as to causal relation. If the histories in this study were changed to exclude injuries, then an entirely different problem would be presented. This cannot be stressed too strongly. The history can reveal the previous cardiac health, the type of accident, the presenting and the bridging symptoms, the time and the character of the cardiac collapse, the amount of healing and the functional capacity of the injured organ. It is needless to emphasize that at present there are no objective measurements of pain, the most common cardiac disabling symptom, which can be judged only from the patient's story.

The courts should realize the importance of the history and accept all testimony which may aid in obtaining a true recital of events. The first recorded history is usually unbiased and contains all the facts and therefore should be given the most weight and consideration, since the needs of the moment and not future benefits were uppermost in the patient's mind at the time the history was given. Subsequent changes in the original story should be accepted with reservations. In the presence of conflicting medical histories lay witnesses should be used to determine just what happened. These histories are occasionally changed through unethical guidance in order to obtain benefits. This practice could easily be discouraged if the courts would accept the first history unless unusual circumstances prevented a recital of the facts. Since the question of causal relation hinges on the history, every effort should be made to obtain the truth.

*Electrocardiographic Considerations.*—The basic lesion is acute cardiac damage, and therefore serial electrocardiograms should show changes immediately after the injury. Such a lesion is not constant and varies as to location, thus producing different kinds of electrocardiographic tracings. The electrocardiographic diagnosis varied in each case, suggesting pericardial or myocardial damage. The electrocardiographic changes in cases of myocardial injury at times were similar to those characteristic of typical and atypical acute coronary occlusion.

*Disability.*—The question of cardiac function in workers is important. Those with a moderate degree of cardiac damage probably recover without any impairment of function (case 5). However, in most of the cases reported here the patients showed a residual disability which varied from total to partial loss of efficiency. Disability is an individual problem and depends on the amount of damage, the degree of healing, the amount of recovery and probably the presence of any underlying pathologic condition.



## CONCLUSIONS

1. Direct nonpenetrating injury of the chest can produce nonfatal disabling heart damage.
2. The resulting disability is due to a combination of structural and functional changes.
3. The clinical picture is that of an acute pathologic condition of the heart and closely resembles that of coronary occlusion, from which it is differentiated by the history.
4. The history is the most important single factor in determining causal relation and the subsequent degree of disability.
5. The electrocardiographic studies are important and usually show changes associated with acute lesions.
6. This clinical syndrome should be considered in the presence of any injury of the chest.

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# STENOSIS OF THE INFUNDIBULUM

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Although stenosis of the pulmonary tract with transposition is one of the most common anomalies encountered in the heart, isolated stenosis of the lower bulbar orifice without transposition is relatively rare. We were able to study clinically over an extended period a patient who on postmortem examination presented this type of anomaly.

## REPORT OF A CASE

*Clinical Observations.*—This woman was first seen by one of us (S. S.) in 1929 at the age of 25. She gave a history of heart disease since birth. She came to inquire as to the advisability of becoming pregnant. Her symptoms were slight dyspnea on exertion for years, moderate swelling of the ankles periodically and easy tiring. She had never been incapacitated because of these complaints. She had had typhoid fever in 1910 and scarlet fever with nephritis in 1916.

Examination in 1929 revealed nothing abnormal except the cardiac condition. On percussion the transverse diameter of the heart was normal. There was dulness, however, 7 cm. to the left of the midsternal line in the second interspace. In the same region were a marked systolic thrill, which was transmitted laterally and slightly upward, and a loud, rough, systolic murmur, transmitted over the entire precordium and back. There was no cyanosis or clubbing of the fingers. The arterial blood pressure was 128 mm. of mercury systolic and 80 mm. diastolic. Roentgen examination revealed the transverse diameter of the heart to be 13 cm., as compared to a transverse chest diameter of 27.5 cm. An electrocardiogram revealed an inverted P wave in lead III (fig. 1). Urinalysis showed nothing abnormal.

The diagnosis at this time was congenital heart disease with patent ductus arteriosus or interventricular septal defect. The patient was told that there was no danger if she became pregnant, and she did so within the year.

Her pregnancy was uneventful, as was her subsequent course (with the exception of an attack of "flu" in 1933 and intermittent headaches) up to May 1938. At that time she noticed fiery red spots on her legs, which faded slowly. In July she began to have chills and a fever, her temperature ranging from 100 to 102 F. These symptoms were accompanied by a feeling of malaise and general aches and pains, as well as some joint pains. In August pains appeared in the chest on the left side, unaccompanied by cough or expectoration. At this time the patient entered the hospital.

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This investigation was aided by a grant from the Otto Baer Fund.

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On admission the cardiac findings were the same as in previous years except that the heart was enlarged to the left and the second heart sound was almost inaudible at the base of the left lung. Petechiae were present in the skin of the legs. There were signs of an infarct in the upper lobe of the left lung posteriorly. The liver was palpable 3 fingerbreadths below the costal margin. The

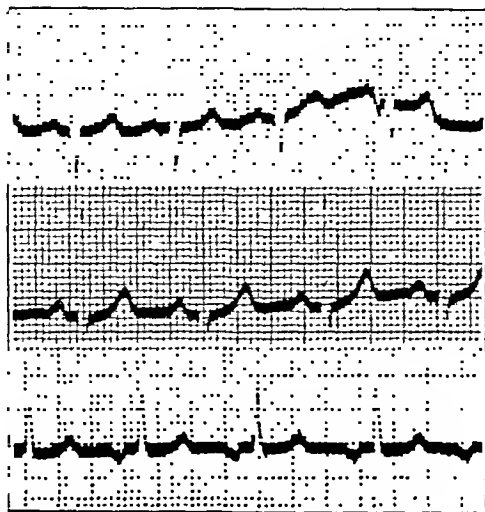


Fig. 1.—Electrocardiogram made on Dec. 17, 1929 (about ten years before death). The only possible abnormality is the inverted P wave in lead III.



Fig. 2.—Teleoroentgenogram made on Aug. 29, 1938 (about one-half year before death). The heart is enlarged; the right border is accentuated, and the left lower pulmonary field is somewhat clouded.

arterial blood pressure was 116 mm. of mercury systolic and 74 mm. diastolic. The erythrocyte count on admission was 4,700,000 per cubic millimeter, which progressively decreased to 3,900,000. The hemoglobin was 80 to 70 per cent. The leukocyte count increased from 8,200 to 15,000 per cubic millimeter, with 60 per cent polymorphonuclear leukocytes. Blood cultures were repeatedly positive for *Streptococcus viridans*. The urine showed occasional red and white blood corpuscles. A roentgenogram taken August 29 (fig. 2) revealed an enlarged

heart with a prominent right auricle and a probable pulmonary infarct in the lower lobe of the left lung.

The diagnosis at that time was subacute bacterial endocarditis (*Str. viridans*) engrafted on a congenital cardiac lesion, probably a patent ductus arteriosus.

During the first week of the patient's stay in the hospital a septic temperature was sustained. The temperature then leveled off for two weeks, only to assume again a febrile, although not typically septic, course, with temperatures ranging between 99 and 101 F. Two weeks after admission sulfanilamide therapy was started. An adequate concentration of sulfanilamide in the blood was reached and was maintained for ten days, but the temperature remained elevated and the blood culture positive for *Str. viridans*. Sodium cacodylate therapy also failed to influence the course of the disease. On September 24 another small pulmonary infarct occurred, and on October 2 the presence of a small cerebral embolus was suspected.

The patient left the hospital on October 15 in fairly good condition with a low grade fever and remained at home in bed. Her course was gradually downhill. From time to time the urine showed erythrocytes and leukocytes. In April 1939 these became much more numerous. At this time she became nauseated and vomited and became dyspneic and somewhat stuporous.

She reentered the hospital on May 15. At this time numerous petechiae were present. The eyelids were puffy. The cardiac findings were the same as previously except that now for the first time a soft, blowing diastolic murmur was heard along the left border of the sternum in the second and the third interspace. The liver extended 4 fingerbreadths below the costal margin on deep inspiration. The spleen was distinctly palpable. There were marked generalized redness, especially over the legs and thighs, and generalized peripheral edema. The urine contained albumin (3 plus), many leukocytes and erythrocytes and an occasional cast. The arterial blood pressure was 118 mm. of mercury systolic and 60 mm. diastolic. The nonprotein nitrogen content of the blood on admission was 82 mg. per hundred cubic centimeters, 118 mg. on May 20 and 120 mg. on May 24, with a creatinine content of 5.4 mg. per hundred cubic centimeters. On May 24 and 25 the patient experienced convulsive seizures involving the right side of the face and the right extremities, with loss of consciousness. On May 26 she died suddenly.

The diagnosis at this time, in addition to the previous diagnosis, was nephritis (focal or diffuse) secondary to bacterial endocarditis. Because of the appearance of a diastolic murmur, the congenital lesion was thought to be a patent ductus arteriosus.

*Postmortem Examination.*—Aside from the condition in the heart, the pathologic diagnosis included (1) subacute splenic hyperplasia; (2) chronic passive hyperemia of the lungs, liver, spleen and kidneys; (3) bilateral hydrothorax, ascites and peripheral edema and (4) acute glomerulonephritis superimposed on a subacute diffuse form of this disorder.

The heart was enlarged, weighing 450 Gm. The arterial trunks emerged in their normal positions. The conus of the right ventricle was bulging and was distinctly demarcated from the right ventricle proper. Its lower portion formed an aneurysmal dilatation measuring 3 cm. in its greatest diameter. The epicardium was dull, granular and covered with fibrin.

The right auricle was dilated and its wall thickened, measuring 1.5 mm. in width. The foramen ovale was closed. The tricuspid orifice was dilated and measured 11 cm. in circumference. The tricuspid valve was normally formed.

However, a firm band extended from the medial end of the anterior leaflet to the firm circular fibrous band to be described. This band had demobilized this portion of the leaflet. The posterior papillary muscle was large, and the anterolateral muscle was relatively small. The mural and the luminal aspects of the anterior leaflet were covered with luxuriant, reddish yellow, semifirm vegetations. Similar smaller and more discrete vegetations were present on the luminal aspect of the medial and the inferior leaflet. Some of the chordae of the anterior leaflet were firm and fibrous



Fig. 3.—*A*, right auricular and ventricular view. Note the vegetations on the tricuspid valve. *B*, right ventricular and infundibular view. The whole infundibulum is filled with vegetations. It is separated from the sinus of the right ventricle by a fibromuscular band, which has been cut into. *C*, left ventricular view. Note that the pars membranacea is markedly thickened. Its inferior border is rolled up to form a systolic pocket. The triangular white rod extends into the defect in the pars membranacea.

The right ventricle was divided into two separate chambers—a superior infundibular outlet portion leading into the pulmonary artery and an inferior main inlet portion communicating with the tricuspid orifice. This division was produced by a firm fibrous band which extended from a point immediately below

the defect in the interventricular septum to be described, in a horizontal direction over the anterior wall of the left ventricle 1 cm. above the anterior leaflet of the tricuspid valve, then back to the septum 1 cm. above the muscle of Lancisi. The lumen produced by this ring measured 1 cm. in diameter.

The lumen of the inferior right ventricular chamber was moderate in size. Its wall, however, was thickened, measuring 0.8 cm. in width. The trabeculae carneae in this chamber were markedly accentuated. The septal muscle bundle began in its usual anterolateral origin and ascended the interventricular septum obliquely to the fibrous ring. It passed behind this ring to continue its course in the superior right ventricular chamber.

The superior infundibular right ventricular chamber was of moderate size. Its wall measured 3 mm. in thickness. The chamber was completely filled with luxuriant vegetations, which had produced the bulge seen externally in the region of the conus. These vegetations were closely adherent to the mural endocardium and to the fibrous ring, where they became continuous with those covering the mural aspect of the anterior tricuspid leaflet, and superiorly to both aspects of the pulmonic valve, extending into the pulmonary artery for a distance of 5 cm. A separate large vegetation lay lodged in the terminal portion of the right pulmonary artery. On removal of the vegetations the remainder of the topography of the muscle bundles of the right ventricle could be discerned. The septal muscle bundle terminated at the base of the septal cusp of the pulmonic valve. The parietal muscle bundle, however, was relatively short, joined the septal muscle bundle at the raphe at the base of the pulmonic valve and terminated inferiorly after a 2 cm. excursion in a well formed recess. The remainder of the anterior wall of the conus could not be well discerned because of the markedly thickened endocardium covered by adherent vegetations.

The pulmonic valve and orifice were normal, and the two pulmonary arteries were given off normally. The ductus arteriosus was closed.

The pulmonary veins and the left auricle were normal. The mitral orifice measured 7.5 cm. in circumference. There were several small, confluent, yellowish gray, granular excrescences at the line of juncture between the anterior and the inferior leaflet of the mitral valve, and several grayish white, smooth, well circumscribed, thickened patches were occasionally encountered.

The left ventricular wall measured 0.9 cm. in greatest thickness. The left ventricular cavity was small in comparison to that of the right ventricle. The pars membranacea was thickened, grayish white and smooth. This thickened region extended upward to involve the right anterior aortic cusp, the posterior basal part of which showed a large, well circumscribed, firm, grayish white, smooth plaque. One millimeter from the base of the right anterior aortic cusp was a defect in the pars membranacea measuring 1 mm. in diameter. From this defect protruded a grayish yellow, friable vegetation.

The aortic orifice measured 5 cm. in diameter. The corpus arantii of each aortic cusp was the seat of a friable, yellowish gray, polypoid vegetation. The aorta was narrow throughout its course. The lining of the aorta was singularly free from plaques. The coronary vessels presented no abnormality.

Microscopically, the myocardium showed marked granular and fatty degeneration. The epicardium presented a thick, fibrinous layer containing clusters of round cells. The vegetations showed many bacteria.

A culture of blood drawn post mortem revealed streptococci (the type could not be subcultured) and *Bacillus coli*.

As far as the heart is concerned the diagnosis included the following conditions: 1. Congenital malformation of the heart, with (*a*) stenosis of the lower infundibular ostium, (*b*) patent interventricular septum in the region of the pars membranacea and (*c*) hypertrophy of the right ventricle proximal to the infundibulum. 2. Acute vegetative endocarditis involving the infundibular portion of the right ventricle; the pulmonic, tricuspid, mitral and aortic valves; the main pulmonary artery, and the endocardium surrounding the opening in the interventricular septum. 3. Acute fibrinous pericarditis. 4. Embolic occlusion of the orifice of the right pulmonary artery by large vegetations and multiple embolic occlusions of the smaller radicles, with the formation of a mycotic aneurysm.

*Comment.*—In retrospect, it is difficult to see how the diagnosis of the cardiac lesion could have been made. When the patient was first seen, ten years before death, a systolic murmur was heard at the base of the left lung. This could have been ascribed to a defect of the interventricular septum, pulmonary stenosis or a patent ductus arteriosus, which may produce only a systolic murmur. In the absence of cyanosis and clubbing and in the absence of a diminution of the P wave in lead II, we did not think we were dealing with pulmonary stenosis. Therefore, in view of the type of murmur, the most likely diagnosis was an interventricular septal defect.

When the patient was seen ten years later, the P wave in lead II was distinctly diminished. In view of the fact that the patient then had subacute bacterial endocarditis and evidence of failure of the muscle on the right side of the heart, the diminution was considered to be due to the failure of this muscle. Thus, the diagnosis still was an interventricular septal defect. On the last admission the appearance of a diastolic murmur in the same region as the systolic murmur still further complicated the picture and made us veer toward the diagnosis of a patent ductus arteriosus.

It is of interest that the patient toward the end of her illness showed signs of uremia. A clinical diagnosis of nephritis secondary to bacterial endocarditis was made, no distinction being drawn between focal and diffuse glomerulonephritis. A diagnosis of diffuse glomerulonephritis might have been more exact, for focal glomerulonephritis (multiple glomerular embolization) is most often not accompanied by an impairment of renal function. Only a few cases of marked glomerular embolization with resultant impairment of renal function have been reported (Bell<sup>1</sup>)

The sudden death of the patient was well explained at postmortem examination by the presence of the large vegetation blocking the right main pulmonary artery.

There remains to be explained the diastolic murmur heard at the base of the left lung on the patient's second admission. The pathologic

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1. Bell, E. T.: *Am. J. Path.* 8:639, 1932.

findings do not clearly account for this murmur. There was a thickening of the base and the body of the right anterior aortic leaflet, as well as vegetations on the valve. Whether this led to a mild aortic regurgitation cannot definitely be stated. It is also possible that terminally there might have been some pulmonary insufficiency due to the dilated pulmonary ring and the involvement of the valve by vegetations.

*Summary.*—A 35 year old woman had congenital heart disease, subacute bacterial endocarditis and acute and subacute glomerulonephritis. The cardiac abnormality consisted of infundibular stenosis with a defect of the interventricular septum. The endocarditis probably began on the defect and spread to the conus. The patient died from the combined effects of heart failure, uremia and toxemia and, finally, from the lodging of a huge vegetative embolus in the right main pulmonary artery.

#### ANATOMIC AND PATHOGENETIC CONSIDERATIONS

From the anatomic standpoint there are various types of conus stenosis, dependent on the size of the infundibulum and the point of stenosis (Keith,<sup>2</sup> Abbott<sup>3</sup> and others). 1. In the least common type (occurring in 19 of 100 cases reported by Keith<sup>2</sup>) the conus is separated from the sinus of the right ventricle by a fibromuscular septum, resulting in two distinct chambers. The point of stenosis is thus at the lower bulbar orifice at the point of junction with the sinus of the right ventricle. About 60 cases of this anomaly have been reported in the literature. 2. In a second group there is an arrest in development of the infundibulum. The infundibular cavity is small and communicates with the sinus of the right ventricle by a small ostium. This is a more common type than the first (occurring in 44 of 100 cases reported by Keith<sup>2</sup>). 3. In the third type there is an almost complete absence of the infundibulum. This is also relatively common.

In almost all cases of the second or the third type of anomaly it is accompanied by transposition. When the stenosis is limited to the lower bulbar orifice, it is more commonly associated with transposition. In the few cases in which transposition does not occur, there is most frequently an accompanying defect or an aneurysm of the interventricular septum. Infundibular stenosis with closed fetal passages is rare.

In the heart we have described it is apparent we are dealing with stenosis of the conus at the lower bulbar ostium with an interventricular septal defect, without transposition of the large arteries.

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2. Keith, A.: *Lancet* 2:359, 433 and 519, 1909.

3. Abbott, M. E.: *Congenital Cardiac Disease*, in Osler, W., and McCrae, T.: *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 612; in *Nelson's Loose Leaf Living Medicine*, New York, Thomas Nelson & Sons, 1937, vol. 4, p. 207.



The various theories propounded as the cause of all types of conus stenosis do not fall within the scope of this report. (see Spitzer,<sup>4</sup> Pernkopf and Wirtinger,<sup>5</sup> and Lev and Saphir<sup>6</sup>). In the isolated type of conus stenosis (without transposition), we must assume that the movements of the heart during the absorption of the bulbus proceeded normally. However, the incorporation of the pulmonic portion of the bulbus into the right ventricle was faulty.

As in our case, most patients with conus stenosis survive to adulthood. When the stenosis is part of a tetralogy, then the patients may die from heart failure. However, many patients with an anomaly of this type and most patients with the isolated type of stenosis die from bacterial endocarditis (Harrison,<sup>7</sup> Eakin and Abbott<sup>8</sup> and Abbott<sup>3</sup>). The vegetations are usually especially luxuriant, as in our case. This has been commented on by Abbott, Harrison and others. No reason has as yet been advanced for the great luxuriance of endocarditic vegetations on the right side of the heart. In 2 cases (1 reported by Clarke<sup>9</sup> and ours), some of these vegetations broke off and produced large pulmonary emboli, blocking the main pulmonary arteries.

#### SUMMARY

A case of infundibular stenosis without transposition is presented from the clinical and the pathologic standpoint. The various types of infundibular stenosis are discussed, and the various theories concerning the pathogenesis of this anomaly are reviewed.

Infundibular stenosis is most frequently part of a tetralogy of Fallot and as such represents the result of an abnormality both in the absorption of the bulbus and in its incorporation into the right ventricle. When stenosis is present without transposition, the absorption of the bulbus must have proceeded normally but its final incorporation into the right ventricle must have been faulty.

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4. Spitzer, A.: *Virchows Arch. f. path. Anat.* **243**:81, 1923.

5. Pernkopf, E., and Wirtinger, W.: *Ztschr. f. Anat. u. Entwcklungsgesch.* **100**:563, 1933.

6. Lev, M., and Saphir, O.: *Congenital Aneurysm of Membranous Septum*, *Arch. Path.* **25**:819 (June) 1938.

7. Harrison, W. F.: *Am. Heart J.* **5**:213, 1929.

8. Eakin, W. W., and Abbott, M. E.: *Am. J. M. Sc.* **186**:860, 1933.

9. Clarke, J. J.: *Tr. Path. Soc. London* **44**:29, 1893.

# RENAL FUNCTION IN DIABETES INSIPIDUS

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Diabetes insipidus and the mechanism of its underlying disturbance have long been a source of interest to investigators. During the last two to three decades a considerable literature has developed along various lines of approach, such as the central nervous system, the endocrine system, the body metabolism and the kidney. It is the last of these that is of particular interest, with specific regard to renal hemodynamics, water exchange and the relation of both to the pituitary.

## REVIEW OF LITERATURE

These three aforementioned aspects of renal function, both in physiologically normal persons and in patients with diabetes insipidus, can be resolved into several fundamental questions: 1. To what extent is the amount of urine excreted a function of (a) renal blood flow or (b) glomerular filtration? 2. (a) What is the relation of the pituitary to urine output as regards both diuresis and antidiuresis? (b) Is the mechanism of its action renal or extrarenal? (c) If the mechanism is renal, to what extent do renal blood flow, glomerular filtration and tubular function play a role?

*Urine Output.*—Relation of Amount of Urine Excreted to Renal Blood Flow: With the Rein<sup>1</sup> thermostromuhr as a means of measuring renal blood flow, Janssen and Rein,<sup>2</sup> using decerebrate dogs, could find no relation between renal blood flow and urine output, while Samaan and Handovsky,<sup>3</sup> using conscious dogs, found that after administration

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This study was aided by the fund for study of renal vascular disease.

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1. Rein, H.: Die Thermo-Stromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefässen in Situ, Ztschr. f. Biol. **87**:394, 1927-1928.

2. Janssen, S., and Rein, H.: Ueber die Zirkulation und Wärmebildung der Niere unter Einfluss von Giften, Arch. f. exper. Path. u. Pharmacol. **128**:107, 1928.

3. (a) Samaan, A.: The Effect of Pituitary (Posterior Lobe) Extract upon the Urinary Flow in Non-Anaesthetized Dogs, J. Physiol. **85**:37, 1935. (b) Handovsky, H., and Samaan, A.: Effet des extraits posthypophysaires sur le

of water an increase in the renal blood flow preceded an increase in urine output. Schmidt and Walker<sup>4</sup> and Walker and associates<sup>5</sup> were in agreement with Janssen and Rein. Van Slyke, Rhoads, Hiller and Alving,<sup>6</sup> using the urea excretion method in dogs, and Chasis, Ranges, Goldring and Smith,<sup>7</sup> using diodrast clearance as a measure of effective renal blood flow in normal human subjects, reported that no relation existed.

**Urine Output and Glomerular Filtration:** The possibility that diuresis could be attributed to an altered rate of glomerular filtration was studied in dogs by means of creatinine clearance as a measure of glomerular filtration by Marshall,<sup>8</sup> Poulsson<sup>9</sup> and Walker and associates,<sup>5</sup> while Chasis and co-workers<sup>7</sup> studied this question in human subjects by means of inulin clearance. No relation between urine output and glomerular filtration rate could be detected by these observers. This is in contrast to the results of Kaplan and Smith,<sup>10</sup> who reported a corresponding change in urine output and glomerular filtration rate in rabbits. In conclusion, it is apparent that the predominance of opinion does not favor a relation between either renal blood flow or rate of glomerular filtration and urine output in the normal physiologic state.

**Relation of the Pituitary to Urine Output.**—Diuresis and Anti-diuresis: The first widely accepted action of pituitary extract was the diuretic effect on the kidney, originally reported in 1901 by Magnus

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débit sanguin rénal et sur la diurèse des chiens normaux et des chiens narcotisés, *Compt. rend. Soc. de biol.* **122**:122, 1936; (c) Observations on the Renal Circulation and Secretion in the Dog with Special Reference to the Effect of Pituitary (Posterior Lobe) Extract, *J. Physiol.* **89**:14, 1937.

4. Schmidt, C. F., and Walker, A. M.: A Thermostromuhr Operating on Storage Battery Current, *Proc. Soc. Exper. Biol. & Med.* **33**:346, 1935.

5. Walker, A. M.; Schmidt, C. F.; Elsom, K. A., and Johnston, C. G.: The Renal Blood Flow in Unanaesthetized Rabbits and Dogs in Diuresis and Anti-diuresis, *Am. J. Physiol.* **118**:95, 1937.

6. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A. S.: Relationship Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis: The Mechanism of Urea Excretion, *Am. J. Physiol.* **109**:336, 1934.

7. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *J. Clin. Investigation* **17**:683, 1938.

8. Marshall, E. K., Jr.: The Influence of Diuresis on the Elimination of Urea, Creatinine, and Chlorides, *J. Pharmacol. & Exper. Therap.* **16**:141, 1920.

9. Poulsson, L. T.: On the Mechanism of Sugar Elimination in Phlorizin, Glycosuria: A Contribution to the Filtration, Reabsorption Theory in Kidney Function, *J. Physiol.* **69**:411, 1930.

10. Kaplan, B. I., and Smith, H. W.: Excretion of Inulin, Creatinine, Xylose and Urea in the Normal Rabbit, *Am. J. Physiol.* **113**:354, 1935.

and Schäfer<sup>11</sup> and later by Schäfer.<sup>12</sup> Recently Heller<sup>13</sup> reviewed this subject and the role of anesthesia in the production of the diuretic effect and reported the separation of the pressor fraction from the antidiuretic factor. He showed that the pressor substance alone is responsible for the diuresis, the effect being of vascular origin, much like that of epinephrine reported by Richards and Plant.<sup>14</sup>

The antidiuretic properties of posterior pituitary extract were not recognized until Frank<sup>15</sup> in 1912 noted an association between injuries to the hypophysis and the state of diabetes insipidus. Simmonds<sup>16</sup> reported 3 cases of polyuria following destruction of the posterior lobe of the pituitary, and Goldzieher,<sup>17</sup> 2 cases. Van der Velden<sup>18</sup> and Farini<sup>19</sup> independently demonstrated the use of posterior pituitary extract in producing antidiuresis. That the same effect could be produced in normal water diuresis was successively demonstrated both in animals and in human subjects by Konschegg and Schuster,<sup>20</sup> Motzfeldt,<sup>21</sup> Rees,<sup>22</sup> Priestley<sup>23</sup> and Weir, Larson and Rowntree.<sup>24</sup>

11. Magnus, R., and Schäfer, E. A.: The Action of Pituitary Extracts upon the Kidney, *J. Physiol.* **9**:27, 1901.

12. Schäfer, E. A. S.: Die Funktionen des Gehirnanhanges (Hypophysis cerebri), Bern, M. Drechsel, 1911.

13. Heller, H.: The Action of the Anti-Diuretic Principle of Posterior Pituitary Extracts on the Urine Excretion of Anaesthetized Animals, *J. Physiol.* **98**:405, 1940.

14. Richards, A. N., and Plant, C. H.: The Action of Minute Doses of Adrenalin and Pituitrin on the Kidney, *Am. J. Physiol.* **59**:191, 1922.

15. Frank, E.: Ueber Beziehungen der Hypophyse zum Diabetes insipidus, *Berl. klin. Wchnschr.* **49**:393, 1912.

16. Simmonds, M.: (a) Hypophysis und Diabetes insipidus, *München. med. Wchnschr.* **60**:127, 1913; (b) Ueber sekundäre Geschwülste des Hirnanhangs und ihre Beziehungen zum Diabetes insipidus, *ibid.* **61**:180, 1914.

17. Goldzieher, M.: Ueber Sektionsbefunde bei Diabetes insipidus, *Verhandl. d. deutsch. path. Gesellsch.* **16**:281, 1913.

18. Van der Velden, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, *Berl. klin. Wchnschr.* **50**:2083, 1913.

19. Farini, A.: Diabete insipido ed opoterapia ipofisario, *Gazz. d. osp.* **34**:1135, 1913.

20. Konschegg, A. V., and Schuster, A. S.: Ueber die Beeinflussung der Diurese durch Hypophysenextracte, *Deutsche med. Wchnschr.* **41**:1091, 1915.

21. Motzfeldt, K.: Experimental Studies on the Relation of the Pituitary Body to Renal Function, *J. Exper. Med.* **25**:153, 1917.

22. Rees, M. H.: The Influence of Pituitary Extracts on the Daily Output of Urine, *Am. J. Physiol.* **45**:471, 1918.

23. Priestley, J. G.: The Regulation of the Excretion of Water by the Kidneys, *J. Physiol.* **55**:305, 1921.

24. Weir, J. F.; Larson, E. E., and Rowntree, L. G.: Studies in Diabetes Insipidus, Water Balance and Water Intoxication: Study I, *Arch. Int. Med.* **29**:306 (March) 1922.

Renal or Extrarenal Mechanism of the Antidiuresis Caused by Administered Posterior Pituitary Extract: It appears that there may be three ways in which the pituitary extract may act in inhibiting urine output. 1. It might affect the water exchange between blood and tissues. This is most easily ruled out, since, first, there is no evidence favoring it and, second, it should actually stimulate diuresis on the basis of plasma dilution (Poulsson,<sup>25</sup> Priestley,<sup>23</sup> Craig,<sup>26</sup> and Underhill and Pack<sup>27</sup>). 2. It might act indirectly through the nervous system and tissues by way of a hypothalamic regulating center, advocated largely by the Viennese school (Molitor and Pick,<sup>28</sup> Mehes and Molitor<sup>29</sup> and Hoff and Wermer<sup>30</sup>). This still requires confirmation. 3. It might act directly on the kidney. This hypothesis was supported by the heart-lung-kidney preparation of Starling and Verney,<sup>31</sup> in which the urine showed the characteristic changes which occur after administration of pituitary extract. It was also supported by the results of Janssen,<sup>32</sup> who showed that direct injection of pituitary extract into the renal artery of one kidney produced a response in that kidney before a similar response occurred in the opposite kidney. This effect was produced despite the ruling out of a nervous mechanism by section of the spinal nerves between the fifth and the sixth cervical vertebra and double vagotomy. This was also corroborated by Verney,<sup>33</sup> Klisiecki and associates<sup>34</sup> and Theobald.<sup>35</sup>

25. Poulsson, L. T.: Ueber die Wirkung des Pituitrins auf die Wasserausscheidung durch die Niere, *Ztschr. f. d. ges. exper. Med.* **71**:577, 1930.

26. Craig, N. S.: The Action of Pituitary Extract on Urinary Secretion, *Quart. J. Exper. Physiol.* **15**:119, 1925.

27. Underhill, F. P., and Pack, G. T.: The Influence of Various Diuretics on the Concentration of the Blood, *Am. J. Physiol.* **66**:519, 1923.

28. Molitor, H., and Pick, E.: Zur Kenntnis der Pituitrinwirkung auf die Diurese, *Arch. f. exper. Path. u. Pharmacol.* **101**:169, 1924; Ueber zentrale Regulation des Wasserwechsels: I. Der Einfluss des Grosshirns auf die Pituitrinhemmung, *ibid.* **107**:180, 1925; III. Ueber den zentralen Angriffspunkt der Diuresehemmung durch Hypophysenextrakte, *ibid.* **112**:113, 1926.

29. Mehes, J., and Molitor, H.: Die Aufhebung der Hypophysin- und Coffeinwirkung durch Stichverletzung der Thalamusgegend, *Wien. klin. Wchnschr.* **39**:1448, 1926.

30. Hoff, H., and Wermer, P.: Untersuchungen über den Mechanismus der Diuresehemmung durch Pituitrin beim Menschen, *Arch. f. exper. Path. u. Pharmacol.* **125**:147, 1927.

31. Starling, E. H., and Verney, E. B.: The Secretion of Urine as Studied on the Isolated Kidney, *Proc. Roy. Soc., London*, s.B **97**:321, 1925.

32. Janssen, S.: Ueber zentrale Wasserregulation und Hypophysenantidiurese, *Arch. f. exper. Path. u. Pharmacol.* **135**:1, 1928.

33. Verney, E. B.: (a) The Secretion of Pituitrin in Mammals, as Shown by Perfusion of the Isolated Kidney of the Dog, *Proc. Roy. Soc., London*, s.B **99**:487,

From still another angle, McIntyre and Van Dyke<sup>36</sup> by a study of the chloride and the bromide distribution between cells and plasma under different conditions controverted the extrarenal mechanism.

Role of Renal Blood Flow, Glomerulus and Tubule Cell in the Production of Antidiuresis: Renal blood flow. Earlier work by Dale,<sup>37</sup> Motzfeldt,<sup>21</sup> King and Stoland,<sup>38</sup> Knowlton and Silverman,<sup>39</sup> Richards and Plant,<sup>14</sup> Priestley<sup>23</sup> and Abel and Geiling<sup>40</sup> produced varying results, with no conclusive evidence that the circulatory mechanism was responsible for antidiuresis, though at times the results were suggestive. Starling and Verney,<sup>31</sup> too, using the isolated perfused kidney, could not attribute the antidiuresis to a vascular effect. Later studies emphasized this. Brings and Molitor<sup>41</sup> noted an initial reduction in the renal volume, which passed off long before the antidiuretic effect. Geiling, Herrick and Essex,<sup>42</sup> Herrick<sup>43</sup> and Walker and associates<sup>5</sup> noted a transient diminution followed by an actual increase in renal blood flow. Samaan and Handovsky<sup>3</sup> apparently made the same observation, disagreeing only in relation to water diuresis, contrary to the citation by

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1926; (b) Die Wasserausscheidung der Säugetierrniere und ihre physiologische Regulation, *Arch. f. exper. Path. u. Pharmakol.* **181**:24, 1936.

34. Klisiecki, A.; Pickford, M.; Rothschild, P., and Verney, E. B.: The Absorption and Excretion of Water by the Mammal: I. The Relation Between Absorption of Water and Its Excretion by the Innervated and Denervated Dog, *Proc. Roy. Soc., London, s.B* **112**:496, 1933.

35. Theobald, G. W.: The Repetition of Certain Experiments on Which Molitor and Pick Base Their Water Centre Hypothesis, and the Effect of Afferent Nerve Stimuli on Water Diuresis, *J. Physiol.* **243**:81, 1934.

36. McIntyre, A. R., and Van Dyke, H. B.: The Distribution and Concentrations of Water and Halides in the Blood and Urine During Diuresis-Inhibition by Pituitary Extract, *J. Pharmacol. & Exper. Therap.* **42**:155, 1931.

37. Dale, H. H.: The Action of Extracts of the Pituitary Body, *Biochem. J.* **4**:427, 1909.

38. King, C. E., and Stoland, O. O.: The Effect of Pituitary Extract on Renal Activity, *Am. J. Physiol.* **32**:405, 1913-1914.

39. Knowlton, F. P., and Silverman, A. C.: The Activity of Pituitary Extract on the Kidney, *Am. J. Physiol.* **47**:1, 1918.

40. Abel, J. J., and Geiling, E. M. K.: A Preliminary Therapeutic Study of the Active Principle of the Infundibular Portion of the Pituitary Gland in Four Cases of Diabetes Insipidus, *J. Pharmacol. & Exper. Therap.* **22**:317, 1924.

41. Brings, L., and Molitor, H.: Ueber die Beziehungen zwischen onkometrisch verzeichneten Groszenänerungen der Niere und Diurese nach Versuchen an der verlagerten Niere, *Arch. f. exper. Path. u. Pharmakol.* **159**:710, 1931.

42. Geiling, E. M. K.; Herrick, J. F., and Essex, H. E.: The Effect of Posterior Pituitary Preparation on the Blood Flow of the Normal Intact Dog, *J. Pharmacol. & Exper. Therap.* **51**:18, 1934.

43. Herrick, J. F. (1938), cited by Corcoran and Page.<sup>45</sup>

Walker and associates <sup>5</sup> and Smith.<sup>44</sup> Corcoran and Page,<sup>45</sup> after measuring renal blood flow indirectly by a modification of the method of Van Slyke and co-workers <sup>6</sup> in which phenolsulfonphthalein (Sheehan <sup>46</sup>) and inulin were used instead of urea, reported a rise in 5 animals and a fall in 4. They could offer no explanation for the inconsistent results. Therefore, the few experiments to the contrary notwithstanding, the effect of pituitary extract on the renal hemodynamics is but transient and cannot account for prolonged antidiuresis.

The glomerulus. Richards and Plant <sup>14</sup> early showed in the rabbit kidney that small doses of solution of posterior pituitary will produce an actual increase in urine output by constricting the efferent arteriole and thereby increasing the intraglomerular pressure. Larger doses, however, produce anuria by also constricting the afferent arteriole. Adolf <sup>47</sup> made similar observations. More elaborate information was sought by the application of clearance tests. Poulsson <sup>25</sup> and Walker and co-workers,<sup>5</sup> using creatinine clearance, and Burgess, Harvey and Marshall,<sup>48</sup> using the xylose and sucrose method of Shannon, Jolliffe and Smith,<sup>49</sup> failed to note any significant decrease in glomerular filtration either in dogs or in human subjects after the administration of solution of posterior pituitary. Gersch,<sup>50</sup> using the ferrocyanide method, was in agreement. Corcoran and Page,<sup>45</sup> on the other hand, employing inulin clearance, noted an increase in the rate of glomerular filtration in the periods of decreased renal blood flow, which suggested constriction of the efferent arterioles. Therefore, from previous evidence one could hardly attribute antidiuresis to an alteration in glomerular function. Special note must be made that apart from the last-named authors, no

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44. Smith, H. W.: *Physiology of the Renal Circulation*, in *Harvey Lectures, 1939-1940*, Baltimore, Williams & Wilkins Company, 1940, pp. 166-222.

45. Corcoran, A. C., and Page, I. H.: *The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance*, *Am. J. Physiol.* **126**: 354, 1939.

46. Sheehan, H. L.: *The Renal Elimination of Phenol Red in the Dog*, *J. Physiol.* **87**:237, 1936.

47. Adolf, E. F.: *How Pituitrin Inhibits Urine Formation*, *Am. J. Physiol.* **116**:1, 1936.

48. Burgess, W. W.; Harvey, A. M., and Marshall, E. K., Jr.: *The Site of Antidiuretic Action of Pituitary Extract*, *J. Pharmacol. & Exper. Therap.* **49**:237, 1933.

49. Shannon, J. A.; Jolliffe, N., and Smith, H. W.: *The Excretion of Urine in the Dog: VI. The Filtration and Excretion of Exogenous Creatinine*, *Am. J. Physiol.* **102**:534, 1932.

50. Gersch, I.: *Reabsorption of Water During Pituitary Anti-Diuresis*, *J. Pharmacol. & Exper. Therap.* **52**:231, 1934.

investigator has been able to obtain positive evidence for an effect of pituitary extract on glomerular function by means of clearance methods.

The tubule cell. Addis and associates<sup>51</sup> early postulated that the inhibitory effect of pituitary extract was due to its specific action on the secreting cell of the kidney. Positive evidence, especially for the proximal portion of the tubule as the site of antidiuretic action, was proposed by Poulsson<sup>25</sup> on the basis of the effect of pituitary extract on urea excretion. Gersch and Stieglitz<sup>52</sup> and Gersch,<sup>50</sup> using the ferrocyanide method, stipulated the loop of Henle, and less so the proximal convolutions, as the site of action, as did Burgess, Harvey and Marshall<sup>48</sup> in their comparative zoologic study of antidiuretic response. The evidence, therefore, favors the position that the pituitary exerts its antidiuretic action on the kidney by its specific effect on the tubule cell.

*Renal Function Under Conditions of Pituitary Deficiency.*—However indefinite is present knowledge of renal physiology in regard to the response of the kidney to administered pituitary extract, all the more uncertain is it when the organism is deprived of that influence. Knowledge of this phase of renal behavior is essential to the better understanding of diabetes insipidus.

Schmitz<sup>53</sup> found the creatinine clearance in 4 cases of diabetes insipidus to be normal and concluded that polyuria is due to a failure in tubular reabsorption of water. White and Heinbecker<sup>54</sup> studied renal function in dogs in which the pars nervosa of the pituitary and the accessory sites of pitressin production were removed. Within two to four weeks after operation they noted a fall both in urea and in creatinine clearance from 30 to 50 per cent, with a return to normal after several months. In later experiments,<sup>55</sup> they noted that the fall in urea clearance was less than that of creatinine clearance and might not fall at all.

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51. Addis, T.; Shevky, A. F., and Bevier, G.: The Regulation of Renal Activity: VII. The Balance Between the Regulation by Adrenalin and by Pituitrin, *Am. J. Physiol.* **46**:129, 1918.

52. Gersch, I., and Stieglitz, E. J.: Histochemical Studies of the Mammalian Kidney: I. The Glomerular Elimination of Ferrocyanide in the Rabbit and Some Related Problems, *Anat. Rec.* **58**:349, 1934.

53. Schmitz, H. L.: The Mechanism of Human Diabetes Insipidus, *J. Clin. Investigation* **16**:675, 1937.

54. White, H. L., and Heinbecker, P.: Hypophyseal Influences in Renal Function and Water Exchange in the Dog, *Am. J. Physiol.* **123**:213, 1938.

55. White, H. L., and Heinbecker, P.: Observations on Creatinine and Urea Clearances on Responses to Water Ingestion and on Concentrating Power of Kidneys in Normal, Diabetes Insipidus and Hypophysectomized Dogs, *Am. J. Physiol.* **123**:566, 1938.



Recently these same authors with an associate <sup>56</sup> carried on studies more closely related to those presented here. In their earlier studies White and Heinbecker <sup>56a</sup> measured the renal function in 2 hypophysectomized dogs by means of inulin and diodrast clearances. They observed both clearances to be one half those found in the normal dog and postulated that though they did not determine the total tubular excretory mass ( $T_m$ ), it, too, was probably one half of normal. In their most recent report White, Heinbecker and Rolf <sup>56b</sup> recorded their observations on 6 hypophysectomized dogs. The diodrast plasma clearance after operation showed an average decrease of more than 40 per cent, with an approximately corresponding drop in the renal plasma flow. Both the plasma diodrast extraction determined from blood drawn from the renal vein and tubular diodrast extraction remained constant in the normal and in the hypophysectomized animals. The glomerular filtration rate decreased correspondingly with the drop in renal plasma flow, while the filtration fraction remained unchanged. The total excretory mass after hypophysectomy was found to be decreased by more than 50 per cent. The total blood volume was decreased by 20 per cent. In view of the unchanged tubular extraction of diodrast at a low plasma level in the face of a definitely decreased total excretory mass, the authors postulated some hypothetic substance concerned in the tubular excretion of diodrast to be deficient in quantity but not in quality. The fall in renal plasma flow is attributed to a combination of a fall in blood volume, diminished cardiac output and uniform renal vasoconstriction.

#### PURPOSE OF STUDY

It was with the application of the inulin and of the diodrast clearance test that the problem of the function of the kidney in diabetes insipidus in human beings was approached. It was hoped, thereby, to shed light on the following questions: 1. What is the state of (*a*) renal blood flow, (*b*) glomerular filtration and (*c*) tubular function in the two well established phases, the untreated, or diuretic, and the treated, or antidiuretic, phase? 2. During the transition from the antidiuretic to the diuretic phase due to the progressive loss of the effect of administered posterior pituitary extract, what relation can be established between renal blood flow and glomerular filtration, on the one hand, and urine output, on the other? 3. What changes, if any, occur in the kidney in a diuretic state

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56. (*a*) White, H. L., and Heinbecker, P.: Observations on Inulin and Diodrast Clearances and on Renal Plasma Flow in Normal and Hypophysectomized Dogs, *Am. J. Physiol.* **130**:464, 1940. (*b*) White, H. L.; Heinbecker, P., and Rolf, D.: Effects of Hypophysectomy on Some Renal Functions, *Proc. Soc. Exper. Biol. & Med.* **46**:44, 1941.

after a single dose of pituitary extract, with its almost instantaneous antidiuretic effect? 4. What changes occur in percentage of plasma volume during this acute transition? 5. Are there observable changes in renal blood flow after administration of water once antidiuresis is established?

#### MATERIAL

In an attempt to answer the foregoing questions, it was possible to study renal function in 7 males with diabetes insipidus. In 6 of them moderate to marked diuresis occurred during the untreated phase. In the seventh patient the diuresis was counteracted by thyroidectomy. A brief outline of each case follows:

CASE 1.—H. N., aged 36, had had diabetes insipidus for fifteen years. The etiology was unknown. The usual fluid intake and output was 10 to 11 liters per day. During treatment with solution of posterior pituitary<sup>57</sup> the fluid exchange fell to 2 to 3 liters per day. The basal metabolic rate was —16 per cent. Except for being somewhat underweight, the patient was essentially normal on physical examination. At the time of this study he was taking solution of posterior pituitary regularly.

CASE 2.—S. T., aged 24, had had diabetes insipidus since early childhood. The etiology was unknown. The fluid intake and output was 11 to 12 liters per day; during treatment with posterior pituitary the fluid exchange decreased to 3 liters. On physical examination the patient appeared essentially normal. At the time of this study he was not taking solution of posterior pituitary regularly.

CASE 3.—F. C., aged 35, had an illness of eleven years' duration which was believed to have followed a streptococcic infection of the throat. The fluid intake and output was 10 to 11 liters per day; during treatment with posterior pituitary the fluid exchange fell to 2 liters. On physical examination the patient was essentially normal. At the time of this study he was not taking posterior pituitary extract regularly, since it induced asthmatic seizures.

CASE 4.—R. D., aged 32, had had diabetes insipidus of unknown etiology for four years. The fluid intake and output was about 10 liters per day; during treatment with pituitary extract the fluid exchange fell to 2 to 3 liters. On physical examination the patient was essentially normal. At the time of this study the patient was not taking solution of posterior pituitary regularly.

CASE 5.—G. A., aged 13, had an illness of four years' duration which was believed to have followed an infection of the middle ear. The fluid intake and output was 10 to 15 liters per day. During treatment with solution of posterior pituitary the fluid exchange decreased to 2 to 3 liters. The patient's growth was moderately stunted, but otherwise physical examination revealed nothing abnormal. At the time of this study he was taking pituitary extract regularly.

CASE 6.—J. K., aged 28, had an illness of nine years' duration of unknown etiology. The fluid intake and output was 8 to 11 liters per day, though shortly before this study it decreased to 6 liters per day. During treatment with solution of posterior pituitary the fluid exchange fell to 2 liters per day. The basal

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57. In all cases during medication and/or experimental procedure solution of posterior pituitary U. S. P. was used.

metabolic rate was —21 per cent. Moderate underdevelopment of the genitalia was present, but otherwise physical examination revealed nothing abnormal. At the time of this study the patient was taking posterior pituitary extract regularly.

CASE 7.—L. R., aged 35, had postencephalitis with parkinsonism and diabetes insipidus of ten years' duration. The fluid intake and output was originally 8 to 10 liters per day. Total thyroidectomy done six years ago was accompanied by a reduction in fluid exchange to 3 liters per day. During the six year period the weight increased from 113 to 203 pounds (51 to 92 Kg.). The basal metabolic rate was —25 per cent.

#### METHOD

Renal blood flow was determined indirectly by measuring the effective plasma clearance of diodrast divided by the percentage of plasma volume, as described by Smith, Goldring and Chasis<sup>58</sup> and Chasis, Ranges, Goldring and Smith.<sup>7</sup> The method essentially depends on the clearance of a substance that is entirely excreted through the glomeruli and tubules in one circulation of renal arterial blood. Maximum clearance is obtained at such plasma concentrations that the ratio of tubular excretion is in direct proportion to the plasma concentration—usually less than 5 mg. per hundred cubic centimeters. Iodine determinations were carried out according to the Smith modification<sup>58</sup> of the Kendall method.<sup>59</sup> The glomerular filtration rate was determined by measuring inulin clearance on the principle that inulin is completely filtered through the glomerulus and only by the glomerulus.<sup>60</sup> The determination of inulin was done according to the method of Alving, Rubin and Miller<sup>61</sup> and their later modification.<sup>62</sup> The total tubular excretory mass ( $T_m$ ) was determined at raised plasma diodrast concentrations,<sup>58</sup> under which circumstance tubular excretion is independent of glomerular activity and renal blood flow and is proportional to the number or mass of actively excreting tubules. It is to be noted that all figures are calculated on the basis of a standard surface area of 1.73 square meters.

In the experiments presented here, the infusions of inulin alone and diodrast in physiologic solution of sodium chloride were prepared in such concentrations

58. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J. Clin. Investigation* **17**:263, 1938.

59. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity: III, *J. Biol. Chem.* **43**:149, 1920.

60. Shannon, J. A., and Smith, H. W.: The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man, *J. Clin. Investigation* **14**:393, 1935. Shannon, J. A.: The Excretion of Inulin by the Dog, *Am. J. Physiol.* **112**:405, 1935; The Excretion of Inulin and Creatinine at Low Urine Flows by the Normal Dog, *ibid.* **114**:362, 1936. Hendrix, J. P.; Westfall, B. B., and Richards, A. K.: Quantitative Studies of Composition of Glomerular Urine: XIV. The Glomerular Excretion of Inulin in Frogs and Necturi, *J. Biol. Chem.* **116**:735, 1936. Richards, A. N.; Bott, P. A., and Westfall, B. B.: Experiments Concerning the Possibility That Inulin Is Secreted by the Renal Tubules, *Am. J. Physiol.* **123**:28, 1938. Smith, Goldring and Chasis.<sup>58</sup> Chasis, Ranges, Goldring and Smith.<sup>7</sup>

61. Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, *J. Biol. Chem.* **127**:609, 1939.

62. Personal communication to the author.

as to give a plasma iodine level of approximately 2 mg. per hundred cubic centimeters in the determination of effective plasma clearance and 30 mg. per hundred cubic centimeters or higher in the determination of the total excretory mass and a plasma inulin level of approximately 10 mg. per hundred cubic centimeters throughout the experiment to determine glomerular filtration rate. The infusion was given intravenously at an average rate of 4 to 5 cc. per minute for twenty to thirty minutes before study to insure equilibrium.

*Preparation of Patients.*—Before any studies were done, these patients were first prepared according to certain routine procedures. (a) A period of hydration of three to four days preceded all experiments. Patients not taking posterior pituitary extract were encouraged to drink abundantly and on the morning of the experiment to drink 1.5 to 3 liters up to ninety minutes before study. This was regarded as essential to counteract possible dehydration. Those patients receiving pituitary extract were also encouraged to take fluids over this same period, though to a more moderate degree, including 1 to 1.5 liters the morning of study. (b) The diuretic phase was established in those patients taking posterior pituitary extract regularly by depriving them of the extract for a minimum of two to three days, till maximum diuresis was attained. In later experiments, this period of deprivation was prolonged to one week. (c) In giving pituitary extract to a patient not taking it regularly a solution of posterior pituitary was administered for three days preceding the experiment in 1 cc. doses subcutaneously,<sup>63</sup> with a minimum of three doses the first day, two the second day and one the morning of the experiment, at which time the antidiuretic effect was well established.

## RESULTS

*Renal Function in Established Diuresis and Antidiuresis.*—The comments on this study can be best made as analyses of individual behavior (table 1).

CASE 1.—The effective plasma clearance on two occasions, following diuresis of seven and, essentially,<sup>64</sup> eighteen days' duration, respectively, was decreased 50 or more per cent compared with that after treatment with posterior pituitary extract for two weeks. On the other hand, after diuresis of two and a half to three days' duration, there was no diminution in clearance. Both the total excretory mass and the glomerular filtration rate were practically constant in all three experiments.

CASE 2.—Effective plasma clearance during the diuretic phase was decreased on the first occasion by 60 per cent and on the second occasion by 30 per cent compared with that after treatment with posterior pituitary extract. In this case also the glomerular filtration rate and the total excretory mass were essentially unchanged.

CASE 3.—On first examination the effective plasma clearance was decreased by 40 per cent compared with that after four days' treatment with posterior pituitary extract. Another study during the diuretic phase revealed a clearance decreased by only 20 per cent. At this time, however, the urine output was only 3.1 cc per minute, which is no greater than that of a nondiabetic person

63. In case 5 the pituitary extract was administered intranasally.

64. The patient took one dose of posterior pituitary extract ten days before study.

TABLE 1.—Effect of Repeated Administration of Posterior Pituitary Extract on Renal Function \*

Case No.	Experiment No.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Effective Blood Flow, Cc./Min.	Filtration Fraction	Total Tubular Excretory Mass, Mg./Min.	Diodrast Clearance/ Tubular Excretory Mass	Inulin Clearance/ Tubular Excretory Mass	Hematocrit Plasma Volume, %	Treatment with Solution of Posterior Pituitary, U. S. P.
			Diodrast	Inulin							
1	1	8.0	304	124.0	724	0.44	37.0	8.3	3.4	41.9	None, 7 days
	2	6.0	381	95.4	735	0.25				51.8	None, 18 days
	3	7.8	750	93.0	1,400	0.12				54.3	None, 4 days
	4	0.72	737	121.0	1,218	0.19	38.1	19.3	3.2	60.5†	3 daily doses, 14 days
2	5	15.0	250	124.0	531	0.19				43.0	None
	6	18.8	416	98.4	816	0.24				51.2	None
	7	18.9	444	109.0	934	0.25	50.0	8.88	2.18	47.5	None
	8	3.0	595	130.0	1,100	0.22	44.12	13.50	2.94	53.7	3 doses 2 days before and 2 doses 1 day before experiment; 1 dose on day of experiment
3	9	4.7	382	104.0	710	0.27	46.5	8.22	2.24	53.8	None
	10	3.1	480	95.3	871	0.20				55.1	None
	11	0.55	600	106.3		0.18	40.24	14.9	2.64		3 daily doses 4 days before experiment, 1 dose on day of experiment
4	12	0.75	483	98.6	792	0.20	29.83	16.2	3.30	60.9	3 daily doses 3 days before experiment, 1 dose on day of experiment
	13	9.8	665	109.0	1,147	0.16	41.8	15.9	2.37	58.0	None, 10 days
5	14	5.0	618	143.0	1,104	0.23				56.0	None, 5 days
	15	1.1	639	80.0 ‡	1,070	0.13	46.8	13.6	1.71	59.7	Extract given
	16	13.5	585	152.0	959	0.26				60.9	None, 2½ days
	17	7.0=15.0§	704	140.2	1,164	0.20				60.5	Extract given

\* The plasma clearance is generally depressed, particularly when pituitary extract has not been administered for some time. The values of maximum difference are set in heavy type. The glomerular filtration rate is practically constant. The total tubular excretory mass shows only slight change.

† This reading was made independently after a week's treatment with pituitary extract.

‡ One cubic centimeter of solution of posterior pituitary was given fourteen minutes before the first period of measurement.

§ The antidiuretic effect of the pituitary extract was lost during the experiment.

with similar preparation and was from one-third to one-half his ordinary output. The glomerular filtration rate was constant. The total excretory mass showed only slight change on one occasion after treatment with pituitary extract and a greater diminution on another. There is no explanation for the latter change, and no significance can be attached to it.

CASE 4.—The effective plasma clearance during two periods of diuresis, for ten and five days, respectively, showed no depression. The glomerular filtration rate on both occasions was also normal. The diminished glomerular filtration rate following treatment with posterior pituitary extract was an acute effect of a dose given fourteen minutes before the experiment; therefore, it is not significant for purposes of this experiment. The total excretory mass, however, was measured well after the acute effect subsided and showed little change in either phase.

CASE 5.—Diuresis could be established for only two days because of the hardship entailed. Despite this, plasma clearance was still decreased by 20 per cent compared with that when the patient was taking posterior pituitary extract. Also, the higher clearance value during medication was obtained despite the progressive loss of antidiuretic effect during the course of the experiment. There was no essential change in the glomerular filtration rate. No measurement of the total excretory mass could be obtained in this case.

CASE 6.—Only limited essential data can be furnished in this case. The plasma clearance following diuresis of two days' duration was within normal range. It is worth noting that the patient's diuresis has recently been improving, with the fluid exchange decreasing from 10 to 6 liters per day. The glomerular filtration rate and the total excretory mass were within normal limits after treatment with posterior pituitary extract. It may also be worth mentioning an approximation that the total excretory mass was higher before medication with pituitary extract than after.

CASE 7 (table 5).<sup>65</sup>—It is to be noted that this patient, having had a total thyroidectomy some time before, was considerably myxedematous, with a basal metabolic rate of —25 per cent and weight of 203 pounds (92 Kg.). His surface area, therefore, was not a true reflection of his renal status. Nevertheless, the renal function was not significantly abnormal.

Generally speaking, therefore, the aforementioned experiments revealed a depression of varying degree in effective plasma clearance during the well established diuretic phase compared with that in the antidiuretic phase, while the glomerular filtration rate and the total excretory mass remained practically constant.

*Acute Effect of Posterior Pituitary Extract on Renal Function* (table 2).—Diuresis was established in all patients for at least two to three days before study. The effective plasma clearance was determined for three or four control periods and was again determined for several more periods after the administration of posterior pituitary extract, the dose varying with the size of the subject. The periods were usually

65. Since completion of this study, this case has been reported at length. (Blotner, H., and Cutler, E. C.: Total Thyroidectomy in the Treatment of Diabetes Insipidus, J. A. M. A. 116:2739 [June 12] 1941).

TABLE 2.—*Acute Effect of Posterior Pituitary Extract on Renal Function\**

Experi- ment Number	Case Number; Date	Period, Min.	Urine Output, Cc./Min.	Diodesat Clear- ance, Cc./Min.	Inulin Clear- ance, Cc./Min.	Filtration Fraction	Dose of Solution of Posterior Pituitary U. S. P., Cc.	Hema- tocrit, Plasma Volume, %	Comment
1	1 3/19/41	(10.0)	6.0	360	90.0	0.25		51.8	B0 †
		Average for 5 periods							
		7.7	4.46	308	69.7	0.23			
		11.8	0.60	216	65.2	0.30	1.0	52.5	B2
		9.3	0.64	416	108.3	0.26		54.1	47 min. after pituitary extract given
2	2 4/8/41	6.7	0.82	448	117.4	0.26			
		(10.8)	18.8	520	(123.0)	0.24		51.2	B0
		Average for 3 periods		Average for 2 periods		Average for 3 periods			
		5.0	18.40	571	159.7	0.28	0.8		
		4.1	5.34	279	75.0	0.27		47.0	B3, drawn 19 min. after pituitary extract given
3	3 3/26/41	4.8	3.42	307	100.4	0.33			
		13.9	2.95	467	121.4	0.26			
		10.6	2.84	561	137.0	0.24			
		10.3	3.29	650	134.0	0.21			
		(11.1)	3.1	490	97.0	0.20		55.1	B0
		Average for 3 periods							
		10.0	3.80	438	93.2	0.21	0.6	56.1	B2
		4.0	1.88	251	54.4	0.22			
		15.3	0.59	318	73.5	0.23		53.0	B4, drawn 48 min. after pituitary extract given
		10.0	0.55	488	98.1	0.20			
		10.4	0.62	579	103.8	0.18			

4	4	(10.0	5.0	600	139.0	0.23	56.0)	B0
		Average for 5 periods						
	2/28/41	6.8	5.42	600	131.0	0.22	1.0	B3, drawn 35 min. after pituitary extract given
		3.7	1.09	800	83.5	0.08	60.0	
		10.9	0.82	872	88.0	0.10		
		11.3	0.89	620	120.0	0.19		
5	5	(11.2	13.5	476	123.0	0.26	60.5)	B0
		Average for 3 periods						
	4/29/41	5.7	11.70	414	113.7	0.27	0.7	B2
		4.8	13.10	670	142.4	0.21	59.7	B3, drawn 32 min. after pituitary extract given
		8.8	1.37	300	69.0	0.23	59.2	
		9.4	3.50	651	138.0	0.21		
		6.8	2.30	443	94.0	0.21	56.5	B4, drawn 60 min. after pituitary extract given
		9.8	2.15	412	92.0	0.22		
6	7	(11.2	3.9	602	105.0	0.17	57.6)	B0
		Average for 4 periods						
	2/14/41	13.2	4.80	585			0.5	
		13.1	2.80	530	90.9	0.17	(middle	
		11.3	0.71	520	98.8	0.19	of period)	B3, drawn 37 min. after pituitary extract given
		12.8	0.55	300	75.8	0.25		
		12.5	0.92	588	117.1	0.20		

\* A marked drop in plasma clearance and in the glomerular filtration rate was accompanied by a rise in the filtration fraction in most cases, indicative of constriction of the afferent arterioles, possibly extending to the afferent arterioles.

† B0 signifies a control sample of blood taken before the experiment. The letter plus a figure denotes the number of the sample taken after the experiment was begun.



shorter after the injection to enable detection of acute changes in function. Samples of blood for hematocrit readings were also taken before and after the injection.<sup>66</sup>

It is to be noted that there is a sharp drop in the glomerular filtration rate in all cases, a corresponding drop in plasma flow in all but case 4 and a rise in the filtration fraction in all but cases 4 and 5. The effect subsided within fifteen to twenty minutes, though antidiuresis persisted. In several cases (1, 2 and 3) it can be noted that the final value for renal plasma flow is even higher than those of the control periods. Hematocrit readings before and after the administration of posterior pituitary extract do not show consistent changes either in direction or in degree.

*Relation of Renal Blood Flow and Glomerular Filtration Rate to Urine Output* (table 3).—The patient studied was G. A., aged 13, in

TABLE 3.—*Relation of Renal Plasma Flow to Increasing Diuresis; Progressive Loss of the Antidiuretic Effect of Posterior Pituitary Extract \**

Case No.	Time, Min.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Filtration Fraction
			Diodrast Clearance	Inulin Clearance	
5 .....	16.9	7.2	608	126.1	0.21
(last dose of solu-	14.8	10.7	530	129.4	0.24
tion of posterior	11.0	12.7	627	128.6	0.21
pituitary U. S. P.	14.1	13.4	518	90.2	0.17
administered intra-	11.9	15.3	582	95.0	0.16
nasally 2½ hr.					
before the experi-					
ment)					

\* The plasma clearance and the glomerular filtration rate remain practically constant despite a progressive rise in the rate of urine output.

whom diuresis was normally severe. He was allowed to take his usual morning dose of posterior pituitary extract, and the experiment was begun two and a half hours later, when there was progressively increasing diuresis corresponding to the loss of antidiuretic effect. It was necessary to use a small catheter (no. 10 F). The study extended over five periods.

Despite the striking increase in urine output from 7 to 15 cc. per minute within the course of one hour, plasma flow and glomerular filtration rate remained practically constant. The somewhat depressed inulin clearance during the last two periods is not significant.

*Effect of Administration of Water on Renal Blood Flow During Antidiuresis* (table 4).—These experiments were continuations of the ones described in the section on "Acute Effect of Posterior Pituitary Extract on Renal Function" and were not begun until it was thought that

66. The tourniquet was not attached to the arm at the time that the blood was withdrawn.

TABLE 4.—*Effect of Administration of Water on Renal Function of Subjects Under the Influence of Posterior Pituitary Extract\**

Case No.; Date	Water Intake, Cc.	Time, Minutes		Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Hema- tocrit, Plasma Volume, %	Comment
		Duration of Period	Interval After Admin- istration of Water		Diurast Clearance	Inulin Clearance		
3 3/26/41	Control Previous 2 periods 1,500 cc. in 15 min.			3.1	490	97	55.1	B0
				0.55	498	98	0.20	B4, drawn before water ingested, 46 min.
				0.62	579	104	0.18	after pituitary extract given
		26.7	5	0.60	512	86.7	0.17	
		13.0	13.7	0.50	575	79.6	0.14	
		16.8	46.8	0.77	453	91.0	0.20	B5, drawn 31 min. after water ingested
		12.4	49.1	0.89	427	90.4	0.21	
		12.5	61.6	0.72	427	85.5	0.20	B6, drawn 76 min. after water ingested
		11.8	73.4	0.77	484	101.0	0.21	B0
		Control Previous period		5.05	600	139	0.230	B3, drawn 35 min. after pituitary extract given
4 2/28/41	1,800 cc. in 6 min.			0.89	620	120	0.193	
				1.02	530	101.0	0.190	
		17.2	5	1.09	534	100.0	0.187	B4, drawn 22 min. after water ingested
		15.7 †	20.7	1.44	573	87.8	0.153	
		16.0	36.7	1.29	573	106.0	0.185	
		14.0	50.7	2.12	555	121.4	0.218	
		10.8	61.5	1.85	612	111.7	0.180	
		8.7	70.2	1.68	547	96.1	0.180	
		9.5	80.1	3.9	578	105	0.17	B0
		Control Previous period		0.92	588	117	0.20	B3, drawn 37 min. after pituitary extract given
7 § 2/14/41	1,100 cc. in 7 min.			0.89	624		57.6	
		35.0	23.0	0.95	542	92.5	58.0	B4, drawn 55 min. after water ingested

\* In all 3 cases a suggestive rise in renal plasma flow occurred after the administration of water. A few grade "diuretic" response is noted especially in case 4 despite an added dose of pituitary extract. The changes in the hematocrit readings are not significant.

† B0 signifies a control sample of blood taken before the experiment. The letter plus a figure denotes the number of the sample taken after the experiment was begun.

‡ An additional 0.5 cc. of solution of posterior pituitary U. S. P. was given in the middle of the experimental period to insure antidiuresis.

§ In this case a total thyroidectomy had been performed six years before this study.

the acute effect of the previously administered pituitary extract had subsided. During the antidiuretic phase, 1 to 1.5 liters of water was given by mouth over a short interval and an attempt made to detect changes in the renal blood flow as a reflection of hyperhydremia. Hematocrit readings were also made.

In cases 1 and 3 there was a slight rise in plasma flow in eighteen and twenty-three minutes, respectively, which promptly subsided to the initial level. In case 2 a repeated smaller dose of posterior pituitary extract was thought necessary to insure antidiuresis just after the administration of water with production of an acute effect, but after twenty-four minutes, well beyond the maximum time of altered clearances in the aforementioned experiments on the acute effect of pituitary extract, the rate of plasma flow was still somewhat elevated. A slight transient depression in glomerular filtration rate can also be noted.

TABLE 5.—*Renal Function After Thyroidectomy* \*

Case No.	Urine Output, Cc./Min.	Plasma Clearance, Cc./Min.		Effective Blood Flow, Cc./Min.	Filtration Fraction	Hematocrit, Plasma Volume, %	Comment
		Diodrast Clearance	Inulin Clearance				
7	3.9	506	88	880	0.17	57.6	No treatment with solution of posterior pituitary

\* The effective plasma clearance and the glomerular filtration rate are within normal limits.

#### COMMENT

*The Tubule Cell as the Site of Pathologic Function in Diabetes Insipidus.*—It is apparent from the data presented that glomerular filtration as measured by inulin clearance is essentially unchanged in the well established diuretic and antidiuretic phases, indicating the absence of any glomerular mechanism in the pathogenesis of diabetes insipidus, as well as the independence of glomerular filtration and urine output in general. This is in complete accord with the studies in diabetes insipidus by Schmitz<sup>53</sup> but not with the animal experiments of White and associates<sup>67</sup> if their studies may be placed on a comparable basis. The last-named authors reported a reduction in glomerular filtration as measured both by creatinine and by inulin clearance in hypophysectomized dogs.

On the basis of the studies presented here it can be reasoned that if the inulin clearance is known to be the same in both phases, the filtrable fraction of diodrast must also be the same, so that whatever variations

67. (a) White and Heinbecker (footnotes 54, 55 and 56a). (b) White, Heinbecker and Rolf.<sup>56b</sup> (c) Heinbecker, P.: Personal communication to the author.

do occur in effective plasma clearance must be attributed to the tubule cells. If one omits case 6, except for a few pertinent remarks later, it will be observed that in all cases other than case 4 the effective plasma clearance is persistently lower when posterior pituitary extract is not given than when it is administered. The clearance under the first-named condition may range from 20 to 60 per cent below the values obtained during medication. If one assumed that practically all the blood flowing through the kidney comes in contact with the clearing mechanism, as there is no obvious morphologic change, microscopically, that would account for a deflection of blood away from it, the depression in clearance can then be explained in one of two ways: 1. There is a decrease in the total blood volume and, hence, in the renal blood flow. 2. There is a specific impairment in the excretory function of the tubule cell.

It is agreed that the first possibility cannot be easily dismissed, since it is imaginable that during the diuretic phase there is a tendency to dehydration and actual depletion of the total blood volume, in turn reflected by decreased renal blood flow. There are several difficulties with this interpretation, however. First, previous water balance studies indicate that during the diuretic phase water intake generally parallels the output, so that the balance is at least approximately maintained.<sup>68</sup> Second, because the possibility of dehydration was fully realized, the patients were encouraged to drink abundantly for several days before study to compensate for diuresis. Third, in case 4 there was no decrease in the renal blood flow despite marked diuresis for two periods of five and ten days, respectively. Fourth, it is difficult to believe that the decrease in total blood volume could be so great as to account for as much as a 60 per cent decrease in renal plasma flow. Finally, the decrease in total blood volume of hypophysectomized dogs which was reported by White, Heinbecker and Rolf<sup>56b</sup> and which was regarded as partially responsible for diminished renal plasma flow was not measured in terms of the original weight of the animals, so that actually the total blood volume was unchanged (Heinbecker<sup>67c</sup>).

The alternative explanation is that the function of the tubule cell is specifically impaired by the deficiency in pituitary hormone manifested not only by the decreased power for the reabsorption of water, with subsequent diuresis, but in its reduced excretory capacity, indicated by the depression in plasma clearance. There are, ostensibly, two ways in which this might be established: 1. Given the conditions of diuresis and low plasma clearance, one should demonstrate a significant improvement in clearance following the administration of a single dose of pituitary extract. 2. During the well established diuretic and anti-diuretic phases, one should demonstrate changes in the total excretory mass corresponding with changes in plasma clearance.

68. Blotner, H.: Unpublished data.

As for the first method of approach, it has been noted in table 2 that in the first 3 cases the terminal clearance values were somewhat above initial control levels after recovery from the acute effect of posterior pituitary extract. This cannot be used as evidence of improved efficiency, however, since comparable results were previously obtained by Geiling and associates,<sup>42</sup> Herrick,<sup>43</sup> Walker and co-workers<sup>5</sup> and Handovsky and Samaan<sup>69</sup> with the use of the thermostromuhr, which ostensibly measures actual blood flow. The sharp rise in case 4 appears attributable to the acute vascular effect of pituitary extract. There is no significant evidence, therefore, that a single dose of pituitary extract will promptly improve the excretory capacity of the tubule cell as it does its capacity for the reabsorption of water.

As for the second method of proof, contrary to the observations of White, Heinbecker and Rolf<sup>56b</sup> with reference to their hypophysectomized dogs, the total excretory mass did not show changes corresponding with those of plasma clearance. In 4 cases in which the total excretory mass was measured both in diuretic and in antidiuretic phases, the difference was slight, if any, generally not exceeding 5 to 6 mg. of iodine per minute, and not consistent in any one direction.

On the other hand, other interpretations may be sought, though here a certain degree of speculation is implied and opposition to certain accepted principles in renal function is met with. In the first instance, it may be stated that the failure of plasma clearance promptly to improve after administration of pituitary extract, is due to the fact that while the restorative capacity of the tubule cell for reabsorbing water is effective and immediate, its capacity for excretion of a solute requiring a greater amount of cell "work" is less effective and delayed. Cell recovery, therefore, requires two factors, (1) sufficient pituitary hormone and (2) sufficient time, both enabling an elevation in the degree of molecular exchange. Once this elevation is established, however, it tends to be retained despite the rapid loss of antidiuretic effect. This will explain the only slight, if any, diminution in plasma clearance in the presence of diuresis of short duration. This is best evident in case 4 and experiment 17 in case 5.

In the second instance, it may be further stated that the failure of the total excretory mass to be depressed during the diuretic phase may be due to the fact that while the tubule cell at the lower level of diodrast concentration necessary for measurement of effective plasma clearance reveals its true state of inefficiency and depressed molecular exchange, at the higher level of diodrast concentration necessary for measurement of the total excretory mass its excretory capacity increases to its normal level of function under the "driving force" of tubule cell saturation.

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69. Handovsky and Samaan (footnote 3 b and c).

Two fundamental observations, however, render this interpretation difficult. First, the concept of impaired tubular excretory function at low plasma diodrast levels apparently implies a decreased extraction ratio of diodrast by the tubule cell. White, Heinbecker and Rolf<sup>56b</sup> have found this to be undiminished in their hypophysectomized dogs. Second, a decreased extraction ratio at low plasma diodrast levels in the face of an undiminished total excretory mass appears contrary to the titration curve as established by Smith, Goldring and Chasis<sup>58</sup> and to the principle more recently stated by Smith.<sup>70</sup> The latter merits quotation.

But whether the retarding factor is conceived as a positive barrier (e. g. impermeable connective tissue) or a negative fault (e. g. failure of the tubule cell to handle all molecules available to it), it would be expected that the retardation would operate on any and all molecules of diodrast with statistical indifference, with the result that the clearance probabilities for any particular molecule would not be increased by increasing the number of molecules.

As to the first point, without intending to offer the following comment as positive proof to the contrary, it is interesting to note that the tubular extraction ratio, as calculated from the tubular diodrast plasma clearance and the renal plasma flow, in experiment 1 compared with that in experiment 4 in case 1 and the ratio in experiment 5 compared with that in experiment 8 in case 2 did show a rise of 0.20 and 0.15, respectively. These cases represented 2 of the 4 most severe instances of diabetes insipidus in the series. The difficulty with offering this as positive proof for diminished tubular extraction is the failure to make the same observation in other instances, particularly in case 2, in which the urinary output was generally marked and pituitary extract not resorted to. On the other hand, even if one grants the contention that decreased plasma clearance is a reflection of actually decreased renal plasma flow, proper interpretation still appears wanting. Of the combination of factors responsible for decreased renal plasma flow proposed by White and associates,<sup>56b</sup> i. e. diminished cardiac output, decreased total blood volume and uniform renal vasoconstriction, the last two have since been withdrawn,<sup>67c</sup> leaving only the first, which, it appears, requires further confirmation. Further, the observation of a diminished total excretory mass in the presence of a normal tubular extraction as indicating the existence of a quantitatively but not qualitatively deficient hypothetic substance appears to imply an "all or none law" of tubule cell function—that at any one time a certain number of tubule cells are not functioning at all. This seems necessary, since there is no other morphologic change, such as fibrosis, to account for a diminution in the total excretory mass. It may be asked why the behavior of the tubule cells, numerically, should

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70. Smith, H. W.: Note on the Interpretation of Clearance Methods in the Diseased Kidney, *J. Clin. Investigation* **20**:634, 1941.

be regarded as different from that of the glomeruli, all of which are believed to function at any one time.<sup>71</sup> Finally, one may question the comparability of function in a hypophysectomized animal with that in a human subject with diabetes insipidus, though, truly, the observations in the former should be highly suggestive.

As to the second criticism, this one cannot be easily dismissed either. It might be contended, however, that these principles apply only to the normal human kidney or the morphologically damaged kidney in which the tubule cell is under adequate hormonal control. Whether the same is true for the kidney in a person with diabetes insipidus may be questioned. Certainly, the observations of White and associates<sup>56b</sup> would corroborate the similarity in behavior.

It is worth noting that the concept of the posterior pituitary controlling the function of the tubule cell in a respect other than water reabsorption has recently been gathering other suggestive support. First, the evidence proposed by Silvette<sup>72</sup> and Silvette and Britton<sup>73</sup> suggested the independence of water reabsorption in relation to chloride. Second, the studies of Harrison and Darrow<sup>74</sup> offered direct proof of the deficiency of chloride reabsorption by the tubules in the absence of adrenal cortex hormone. This, according to the belief expressed by Silvette and Britton, lends credence to the antagonism between the pituitary and the adrenal cortex hormones occurring within the tubular epithelium.

In conclusion, from the data presented here it is difficult to consider diminished plasma diodrast clearance as absolute proof of a diminution of tubular excretory function, though there is suggestive evidence in at least 2 instances to the contrary. Certainly, if the interpretation of these observations were based solely on the diminution of total renal plasma flow, the clearances would indicate a normally functioning kidney. However, until more basis for this is obtained and the subject pursued to its more logical conclusion, some doubt will persist.

*Effect of Posterior Pituitary Extract on the Glomerulus.*—It has already been noted (table 1) that during the well established diuretic

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71. Smith, H. W.: Studies in the Physiology of the Kidneys, in Porter Lecture Series, no. 9, Lawrence, University of Kansas, University Extension Division, 1939, p. 89.

72. Silvette, H.: The Influence of Post-Pituitary Extract on the Excretion of Water and Chlorides by the Renal Tubules, *Am. J. Physiol.* **128**:747, 1940.

73. Silvette, H., and Britton, S. W.: Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Posterior Pituitary Action, *Am. J. Physiol.* **123**:630, 1938.

74. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, *J. Clin. Investigation* **17**:505, 1938; Renal Function in Experimental Adrenal Insufficiency, *Am. J. Physiol.* **125**:631, 1939.

and antidiuretic phases the glomerular filtration rate is practically constant. As to the acute effect of pituitary extract, previous investigators,<sup>75</sup> applying various clearance methods other than that used by Corcoran and Page,<sup>45</sup> could not detect any significant change in the glomerular filtration rate. It should be stated, however, that Richards and Plant<sup>14</sup> and Adolf<sup>47</sup> early demonstrated, by other methods, that small doses of solution of posterior pituitary produced a pure constriction of the efferent arteriole, with maintenance of or rise in the glomerular filtration rate, while large doses extended this constriction to the afferent arteriole as well.

In table 2 it can be seen that in practically all cases there was a prompt significant drop both in glomerular filtration rate and in renal plasma flow, as much as 50 per cent or more, with an associated rise in filtration fraction, which gradually returned to its original level within fifteen to twenty minutes. If one bases one's reasoning on the work of Chasis, Ranges, Goldring and Smith,<sup>7</sup> it is fair to assume that the effect observed here after the administration of pituitary extract is due to a predominant constriction of the efferent arteriole. In view of the marked decrease in glomerular filtration rate, it is believed that this constriction may involve the afferent arteriole as well. This would be in accord with the results reported by Richards and Plant<sup>14</sup> when they used large doses of solution of posterior pituitary, to which the doses used here are comparable. The reason for the unique behavior in case 4 is not clear. It is concluded that pituitary extract in relatively large doses will produce a predominant constriction of the efferent arteriole and that its effect will possibly extend to the afferent arteriole.

*Effect of Posterior Pituitary Extract on Renal Blood Flow.*—The considerable disagreement among early workers<sup>76</sup> on this problem has already been noted. Later investigators<sup>77</sup> were more in agreement that there is a slight initial transient diminution in renal blood flow, which returns to the original level or to an even higher one. In the cases presented here, except case 4, posterior pituitary extract produced a sharp, significant drop in the renal blood flow, as much as 50 per cent or more, which returned to its original level within fifteen to twenty minutes and in the first 3 cases eventually reached a level above that of the control period. The suggestion of the supposed causal relation between renal blood flow and antidiuresis attributed to Handovsky and

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75. Walker, Schmidt, Elsom and Johnston.<sup>5</sup> Poulsson.<sup>25</sup> Burgess, Harvey and Marshall.<sup>48</sup> Gersch.<sup>50</sup>

76. Richards and Plant.<sup>14</sup> Motzfeldt.<sup>21</sup> Priestley.<sup>23</sup> Dale.<sup>37</sup> King and Stotland.<sup>38</sup> Knowlton and Silverman.<sup>39</sup> Abel and Geiling.<sup>40</sup>

77. Handovsky and Samaan.<sup>69</sup> Walker, Schmidt, Elsom and Johnston.<sup>5</sup> Brings and Molitor.<sup>41</sup> Geiling, Herrick and Essex.<sup>42</sup> Herrick.<sup>43</sup> Corcoran and Page.<sup>45</sup>



Samaan,<sup>69</sup> by Walker and associates,<sup>5</sup> and explained by the last-named authors as due to the intravenous route of administration of pituitary extract does not appear to be a valid argument, since the injections in the study reported here were all given subcutaneously, yet the drop in renal blood flow was sharp. As for the relation of renal blood flow to antidiuresis, it is obvious that this is not a factor, since antidiuresis persists despite the eventually raised rate of renal blood flow.

It is worth noting that in case 7 as in the other cases, despite thyroidectomy, the acute effect of posterior pituitary extract was much the same in relation both to the glomerular filtration rate and to the renal blood flow except for a moderate prolongation of the latent period till maximum response was obtained. This slowed response may be due to the combined effect of the presence of myxedema, hence slower absorption, and the smaller dose (0.5 cc.) of extract used. It appears, therefore, that the absence of the thyroid does not alter the acute action of pituitary extract and that the effective plasma clearance is within normal range.

*Relationship of Renal Plasma Flow and Glomerular Filtration to Urine Output.*—Case 5 offered the opportunity of studying the relation of renal blood flow and glomerular filtration to urine output from a slightly different standpoint from that used by other investigators. Chasis, Ranges, Goldring and Smith<sup>7</sup> and other authors previously studied this relation by administering water to a subject and noting the state of these two factors during the resulting period of water diuresis. In the study presented here, the conditions were reversed. The patient was initially under the antidiuretic control of pituitary extract, which was allowed to diminish with progressively increasing diuresis until the initial volume of urine was more than doubled during the course of the experiment (table 3). This approach offered the advantage of avoiding any extrinsic factors associated with the oral administration of a large amount of fluid. It is noteworthy that despite the markedly increasing diuresis, the renal plasma flow and the glomerular filtration rate were practically constant throughout. This offers further confirmation that renal blood flow and glomerular filtration, on the one hand, and urine output, on the other, are entirely independent of one another. By deduction, one may infer that water excretion must be dependent solely on the state of tubular reabsorption.

*Relation of Renal Blood Flow to the Administration of Water During Antidiuresis.*—It was originally thought possible to make distinctive observations on (1) the production of an accentuated hydremia following water administration, as manifested by changes in the renal blood flow, while the subject was under the antidiuretic influence of posterior pituitary extract; (2) the presence of a diuretic response to water under

antidiuretic conditions, and (3) the demonstration of a relation between the peak of the water load and the diuretic response.

In the past many different methods have been used, but most consistent results have been recently obtained by means of gravimetric estimation of total solids and changes in electrical conductivity of serum. These have been reviewed at some length by Findley and White.<sup>78</sup> The consensus of later opinion favored a slight transient hyperhydremia, with a latent period between the peak of the water load and the diuretic response. Since then, Handovsky and Samaan,<sup>69</sup> studying renal blood flow by means of the thermostromuhr, detected a rise after the administration of water and actually attributed diuresis to the stimulus of hyperhydremia. Chasis, Ranges, Goldring and Smith,<sup>7</sup> using diodrast clearance in normal human subjects, could not detect any rise in renal plasma flow related to water diuresis.

The result of the studies undertaken here have proved disappointing. In 3 cases a slight transient rise occurred in the renal plasma flow, but it was not sufficient to be more than suggestive. Similarly, no conclusions can be safely drawn on the relation of the peak of the water load to the diuretic response.

As for the diuretic response, the impression gained is that a low grade "diuretic" curve occurs within fifty to sixty minutes, best demonstrated in case 2, in which it may also be pointed out that the repeated dose of pituitary extract did not produce further depression in the urine output or affect the shape of the curve. In case 3 the complete curve is not noted, but here, too, there was a low grade diuretic response. In conclusion, then, the studies presented only suggest that after administration of water to a person under the antidiuretic influence of pituitary extract, a transient hyperhydremia is followed by a low grade "diuretic" response.

*Hematocrit Reading in Relation to Posterior Pituitary Extract.*—It was thought that during study of the acute effect of pituitary extract on renal function, with or without the administration of water, characteristic changes in the hematocrit reading might be detected. Previously Underhill and Pack<sup>27</sup> and Craig<sup>26</sup> noted a definite reduction in the percentage of hemoglobin in the blood of dogs after the administration of solution of posterior pituitary without and with administration of water. The observations cited in table 4 did not prove as definite. The highly encouraging result obtained in the first case studied (case 4, table 2), a rise of 4 per cent in the plasma volume in thirty-seven minutes after the injection of pituitary extract, was not borne out in the other cases. Thus, in cases 1

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78. Findley, T., Jr., and White, H. L.: Response of Normal Individuals and Patients with Diabetes Insipidus to the Ingestion of Water, *J. Clin. Investigation* 16:197, 1937.

and 6 the rise was slight but not significant, while in cases 2, 3 and 5 there was a fall up to 4 per cent (table 2). Even in those cases in which water was administered while the subject was under the influence of pituitary extract (table 4), there was no significant change, except in case 1, in which instance it must be realized that the rise occurred from the lowest depressed point following the injection of pituitary extract. As for the hematocrit reading during the well established diuretic and antidiuretic phases (table 1), it may appear that in a general way, the highest percentage of plasma volume accompanies the highest plasma clearance and vice versa. Careful scrutiny, however, will reveal instances in which the hematocrit difference is slight with a disproportionate difference in clearance or is significant with no difference in plasma clearance. No conclusions, therefore, can be drawn from the foregoing observations on the relation of pituitary extract to the hematocrit reading.

#### SUMMARY AND CONCLUSIONS

The renal function in 7 cases of diabetes insipidus (in 1 case total thyroidectomy had been performed) was studied by means of inulin and diodrast clearances with the intention of establishing the site of pathologic change in terms of function.

The comparison of function during the well established diuretic phase with that during the antidiuretic phase revealed a decrease in effective plasma clearance in the diuretic phase, in most instances from 20 to 60 per cent below clearance during the antidiuretic phase. This did not tend to be true if the diuresis was of short duration. The glomerular filtration rate and the total excretory mass ( $T_m$ ) were relatively constant in both phases. It might be suggested that the decrease in plasma clearance is due to an impairment in the excretory function of the tubule cell which is restored under the influence of repeated administration of solution of posterior pituitary. Also, the constancy of the total excretory mass during the diuretic phase might be explained by the elevation of functional level under the "drive" of tubule cell saturation. However, absolute proof of this cannot be offered from the data obtained. Besides, data from other studies controvert this interpretation. That decreased total blood volume may cause decreased clearance is not altogether ruled out, though it is not felt to be the responsible factor.

The administration of solution of posterior pituitary, producing an acute transition from diuretic to antidiuretic phase, was accompanied by a sharp drop in the glomerular filtration rate and in the renal plasma flow, with a rise in the filtration fraction. The acute effect subsided within fifteen to twenty minutes, with the plasma flow in 3 of 5 cases eventually reaching a level above that of the control period. The effect

is believed due to a predominant constriction of the efferent arterioles, possibly extending to the afferent arterioles.

The study of the relation of renal plasma flow and glomerular filtration to urine output during the course of progressively increasing diuresis with corresponding loss of the antidiuretic effect of posterior pituitary extract revealed their independence of one another. This offers corroboration for the hypothesis that excretion of water is a function of tubular reabsorption.

Suggestive evidence is presented for the occurrence of a transient hyperhydremia and a low grade "diuretic" response following the administration of water to a subject under the antidiuretic influence of posterior pituitary extract.

There appears to be no consistent change in the hematocrit reading following administration of solution of posterior pituitary with or without the administration of water.

Dr. Harry Blotner cooperated in securing the case material studied and permitted me to make use of his clinical records; Drs. Soma Weiss, James P. O'Hare, G. Philip Grabfield and Allen M. Butler contributed suggestions; Drs. Homer W. Smith, James A. Shannon and Alf S. Alving gave counsel in questions of technic, and Miss Betty Eichorn gave technical assistance.

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS  
WITHOUT CUTANEOUS MANIFESTATIONS AND WITH HERETOFORE  
UNDESCRIBED PULMONARY LESIONS

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As more and more observations are recorded on the clinical syndromes of acute disseminated lupus erythematosus and atypical verrucous endocarditis, it becomes more apparent that they constitute slightly varying but confusing manifestations of the same disease. These observations include the erythema group of cutaneous diseases with visceral manifestations first clearly pointed out by Osler<sup>1</sup> in 1904; the atypical verrucous endocarditis recognized by Libman in 1911 and reported more fully by Libman and Sacks<sup>2</sup> in 1924; the polyserositis, polyarthritis and glomerulonephritis with long-continued fever described by Christian<sup>3</sup>; a diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis, reported by Baehr and associates<sup>4</sup> in 1935; the nonbacterial thrombotic endocarditis accompanied by prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions described by Friedberg, Gross and Wallach<sup>5</sup> in 1936, and the generalized capillary and arteriolar thrombosis described by

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From the Kingston Hospital (Dr. Rakov) and the City of Kingston Laboratories (Dr. Taylor).

1. Osler, W.: On the Visceral Manifestations of the Erythema Group of Skin Diseases, *Am. J. M. Sc.* **127**:1 (Jan.) 1904.

2. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33**:701 (June) 1924.

3. Christian, H. A.: Long Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology, *M. Clin. North America* **18**:1023 (Jan.) 1935.

4. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), *Tr. A. Am. Physicians* **50**:139, 1935.

5. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, *Arch. Int. Med.* **58**:662 (Oct.) 1936.

Gitlow and Goldmark<sup>6</sup> in 1939. The Reifenshteins<sup>7</sup> have pointed out this relation in a convincing manner; Osler long before them stated that while a great number of the erythemas, including simple erythema, erythema exudativum, herpes iris, erythema nodosum, certain of the purpuras, urticaria and angioneurotic edema, are usually described as separate diseases, they belong to one family, and he characterized them as follows:

. . . by the similarity of the conditions under which they occur, the frequency with which the lesions are substituted the one for the other in the same patient at different times, the tendency to recurrence, often through a long period of years, and lastly, the identity of the visceral manifestations.

It is fairly clear that a diffuse vascular process involving the smaller blood vessels of the skin and the viscera is the essential lesion of these signs and symptoms. Because in all of these clinical syndromes cutaneous lesions at some time are erythematous and widespread, they are now classified as lupus erythematosus disseminatus. This disease most frequently suggests itself to the observer because of the very complexity of its manifestations. At times it simulates acute rheumatic fever, subacute bacterial endocarditis and polyserositis with subacute glomerulonephritis, yet never quite fulfils the diagnostic criteria of any one of these disorders. The prolonged fever, polyarthrititis, polyserositis, evidence of endocarditis and tendency toward remissions frequently lead to the diagnosis of the rheumatic state. Endocarditis, erythematous cutaneous nodules, nephritis and anemia, especially when white-centered petechiae appear, point strongly to the diagnosis of endocarditis lenta. The long-continued fever with conspicuous involvement of the serous cavities and synovial membranes and the eventual glomerulonephritis without signs of endocarditis may lead to a diagnosis of subacute Pick's disease.<sup>8</sup>

But to one who observes the condition from day to day the persistent leukocytopenia, cutaneous rash, white-centered petechiae and nephritis make the diagnosis of rheumatic fever untenable. Likewise the presence

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6. Gitlow, S., and Goldmark, C.: Generalized Capillary and Arteriolar Thrombosis: Report of Two Cases with a Discussion of the Literature, *Ann. Int. Med.* **13**:1046 (Dec.) 1939.

7. Reifenstein, E.; Reifenstein, E., Jr., and Reifenstein, G.: A Variable Symptom Complex of Undetermined Etiology with Fatal Termination (Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian) and Diffuse Peripheral Vascular Disease (Baehr and Others), *Arch. Int. Med.* **63**:553 (March) 1939.

8. Tremaine, M. J.: Subacute Pick's Disease (Polyserositis) with Polyarthrititis and Glomerulonephritis, *New England J. Med.* **211**:754 (Oct. 25) 1934.

of acute pericarditis and polyserositis with blood cultures persistently negative for growth and the presence of leukocytopenia are incompatible with the diagnosis of subacute bacterial endocarditis. The cutaneous rash, polyarthritis, leukocytopenia and nephritis rule out Pick's classic pericarditic pseudocirrhosis of the liver, but because of the prominent adhesive pericarditis and polyserositis the syndrome has been classified as subacute Pick's disease with polyarthritis and glomerulonephritis. And so we might continue with the remainder of these protean syndromes of unknown origin bearing close resemblance to many infectious diseases and encumbered with lengthy titles which only add confusion to the nomenclature and diagnosis. A careful analysis of the clinical and pathologic data seems to indicate that all are intimately related and that the essential lesion is endotheliitis almost always accompanied by polymorphous cutaneous lesions.

The possibility that acute disseminated lupus erythematosus may appear and run its fatal course without cutaneous manifestations has frequently been mentioned, but no authenticated cases have been reported in which the cutaneous lesions did not appear at some time. Moreover, only rarely has an observer appreciated that pulmonary parenchymal lesions are specifically a part of the visceral manifestations of this disease. The clinical signs are those of long-standing consolidation, and this must be distinctly differentiated from the almost universal terminal pyogenic infection of the lungs. A proper evaluation of these pulmonary lesions seems to have been made by Osler<sup>1</sup> (case 26) and later by Tremaine<sup>8</sup> (case 2). Osler stated:

On December 27 [the patient] . . . had a chill and on the third day consolidation of the left lower lobe was found. Then the other lung became involved [26th day]. . . . The right lung has been clearing [3 weeks later]. The left lower lobe has been solid for some weeks. I put a needle in two places, but got nothing.

Tremaine reported:

Throughout the four months [the patient] . . . remained in the hospital there were frequent bouts of fever, chills and joint pains. The physical signs of a small amount of fluid at the bases of both lungs, and of consolidation at the inferior angle of the left scapula were usually present. A right thoracentesis yielded 75 cc. of fluid but no organisms.

We feel that a case of acute disseminated lupus erythematosus in which we observed the patient through a long clinical course without her exhibiting at any time a characteristic rash, a unique circumstance, should be reported. Furthermore, the long-continued consolidation of the lungs leads us to believe that the pulmonary parenchymal changes are an integral part of the disease, comparable to those encountered in the other viscera.

## REPORT OF A CASE

F. N., a 24 year old white woman, whose mother died when 34 years old of rheumatic heart disease, had been healthy until Dec. 10, 1939, when she noted arthralgia and numbness of her extremities. Three weeks later a physician prescribed salicylates, but the symptoms continued unabated, yet she was able to carry on her work as an examiner in a pajama factory. On Jan. 8, 1940 she experienced severe pain over the precordium extending into the left axilla, after which she became thirsty and drank increasing amounts of water. Nervousness, insomnia, asthenia and dyspnea followed in rapid succession, and she lost some weight but had no cough and experienced no night sweats. She was first seen by one of us (H. L. R.) on January 29, and because of signs of consolidation at the base of the left lung, hospitalization was advised.

On admission to the Kingston Hospital, the patient was not acutely ill, the temperature was 101.2 F., the pulse was 140 per minute and regular, the respirations were 32 per minute but not labored and the blood pressure was 84 systolic and 60 to 58 diastolic, measured in millimeters of mercury. Signs of consolidation at the base of the left lung, confirmed roentgenologically, were present. There were 5,600 white cells per cubic millimeter of blood and severe secondary anemia. The urinary sediment contained a few pus cells and a rare erythrocyte. The scanty sputum contained no acid-fast bacilli, but pneumococci of types XIX, XX and XXIV were present. Blood cultures yielded no growth after nine days' incubation.

After two days' administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) the concentration of the free drug in the blood was 5.5 mg. per hundred cubic centimeters, but to our astonishment the patient's condition grew worse rapidly. On February 3, the temperature had risen to 104.8 F., the pulse rate was 160 and the respiratory rate was 40 per minute, and she was placed in an oxygen tent. A thoracentesis on the left side yielded a small amount of sero-sanguineous fluid, from which no organisms could be isolated.

An electrocardiogram revealed low voltage with a slightly elevated ST junction in lead I, and the ascending limb of the ST segment was concave. Sinus tachycardia was evident, but there were no changes of significance in the remaining leads. These observations suggested acute pericarditis. Physical signs of pericarditis were noted after forty-eight hours, together with an inconstant slight mitral systolic murmur, and although the temperature had subsided to 101.2 F., the tachycardia and tachypnea persisted; no signs of congestive heart failure appeared.

On February 8 the murmur and the signs of pericarditis had disappeared, but evidence of consolidation at the base of the right lung was present for the first time and the temperature again rose to 104.8 F. There was change in the area of consolidation in the left lung, with numerous crepitant rales audible in the area radiating from the precordium to the left axilla. In view of the fact that adequate sulfapyridine therapy accompanied by repeated transfusions of blood failed to produce a clinical response over a period of ten days, the chemotherapy was stopped. The persistent leukocytopenia with the high fever and signs of pneumonitis and pericarditis seemed paradoxical. It was felt at this time that the following observations pointed to the diagnosis of acute disseminated lupus erythematosus in spite of the fact that there were no cutaneous manifestations: arthralgia, pleuritis, pericarditis, pneumonitis, leukocytopenia with high fever, sterile blood cultures and total absence of favorable response to adequate therapy for pneumococcic infection.



A remittant fever persisted, and the temperature reached its peak of 105.4 F. on February 14, then gradually subsided to 99 F. on February 20. The patient's condition improved, and on February 22 she was removed from the oxygen tent. Not only did the signs of consolidation persist in the bases of the lungs, but the temperature rose during the next few days to 103 F. and remained elevated for another week, after which it fluctuated between 99 and 100.2 F. until March 6, when it returned to normal. At no time was splenomegaly present, and petechiae were never observed. The blood pressure persisted at a low level. Repeated blood cultures were negative for growth. Examination of the urine always revealed a few blood cells, many pus cells and albumin, yet there was never any nitrogen retention in the blood. The erythrocyte sedimentation rate was persistently accelerated; the thrombocytes remained at a normal level, and serologic reactions for syphilis were negative.

On discharge from the hospital on April 19, the respiratory rate was normal, but the tachycardia and signs of consolidation of the lungs were still present. An electrocardiogram made at this time showed low voltage and an isoelectric T wave in lead I and inverted T waves in leads II, III and IV-F, which was considered indicative of chronic adhesive pericarditis. The signs of persistent consolidation at the bases of both lungs were erroneously considered to be Ewart's sign in spite of bilateral involvement and our failure to demonstrate physical and roentgenologic signs of massive pericardial effusion. That these signs were the result of pneumonia seemed unlikely; instead they were thought to be evidence of persistent pulmonary atelectasis, resulting from earlier pericardial effusion. Carbon dioxide inhalations had not effected an expansion. The final diagnosis on discharge rested between rheumatic fever with pericarditis and acute disseminated lupus erythematosus.

For five months after her discharge the patient was afebrile. However, in spite of constant rest in bed the pulse rate remained rapid; she failed to gain weight, remained asthenic and was slightly dyspneic. During this interval, the signs of consolidation at the bases of the lungs persisted, but there was no cough, and no murmurs or adventitious sounds were heard on auscultation over the precordium. The rate of erythrocyte sedimentation continued rapid. Electrocardiograms revealed inversion of the T wave in all four leads but no prolongation of the PR interval. Mantoux and patch tests for tuberculosis gave negative results. The urine contained a few pus cells in the sediment. Roentgenograms of the chest made on June 3 showed the cardiac silhouette to be of normal size with obliteration of the costophrenic angles by shadows of increased density indicative of pleural involvement, and above this the pulmonary fields appeared clear except for a slight thickening of the lung root. Mild secondary anemia persisted but at no time was there leukocytosis. No cutaneous manifestations appeared even after prolonged exposure to sunlight.

Early in September 1940, after an episode of pharyngitis, the patient again became febrile and dyspneic. On her second admission to the hospital, September 18, the temperature was 103.2 F., the pulse rate was 130 per minute and regular and the respiratory rate was 38 per minute. There was slight cyanosis of the finger tips and the lips, with beginning clubbing of the fingers. Her dyspnea was only slightly relieved by oxygen. The white cell count was now 3,700 per cubic millimeter of blood, with 80 per cent polymorphonuclears, and the sedimentation rate of erythrocytes was still rapid. The electrocardiogram now showed low voltage in lead I with a slightly elevated concave ST segment, upright T waves in leads II and IV and an inverted T wave only in lead III. This was regarded as evidence of superimposition of the pattern of acute peri-

carditis on a previous pattern of chronic adhesive pericarditis. Repeated blood cultures remained sterile after fourteen days' incubation. Again red blood cells, pus cells and albumin were found in the urine, but there was no elevation of the blood nonprotein nitrogen. The blood pressure was 86 systolic and 60 diastolic. The cardiac shadow was slightly larger than on previous roentgen examinations; the pulmonary conus was more prominent; the left costophrenic angle was obliterated, and the infiltration of the right lower bronchial tree was increased, but far less than the tubular breathing and the egophony at the areas in the bases of the lungs led one to believe. On auscultation over the precordium only a gallop rhythm was noted. Splenomegaly and lymphadenopathy were not observed. The patient's condition became progressively more grave, with the temperature fluctuating between 102 and 104.4 F., until her death on September 30.

The final diagnosis lay between the rheumatic state and lupus erythematosus disseminatus. We felt that the rheumatic state was the more likely condition.

*Necropsy.*—The skin of the body was tanned over the exposed parts; elsewhere it was white. The ankles and the dorsum of each foot seemed a little swollen, but there was no edema of the pitting variety. In the abdominal cavity there was a small amount of free fluid. A moderately enlarged spleen was bound to the abdominal wall and the under surface of the left lobe of the liver by extensive, friable adhesions. Likewise the liver, which was not enlarged, was covered by adhesions, similar to those over the spleen. The stomach and the intestines showed nothing striking. The liver markings were distinct, the tissue was dark, and a few small yellow areas were present. The enlarged spleen was four times its normal size and had conspicuous malpighian bodies and a pulp which was firm. It in no way resembled the spleen of hemolytic jaundice or of bacterial endocarditis. The kidneys showed no abnormalities other than a few definite petechial hemorrhages in the cortex. The pelvic organs were not remarkable, and only a small corpus luteum of menstruation was present in one ovary.

The most extensive, and perhaps most significant, changes were found in the thoracic cavity, where the entire pleural spaces were obliterated by easily separated adhesions like those over the spleen and liver. The lungs were small and atelectatic. Particularly was this true of the lower lobes which no longer extended into the costophrenic angles of the pleural cavities but were rigidly held in an atelectatic state high on the diaphragm by the adhesions just described. These adhesions were not edematous. A careful exploration of the major bronchi and their minor branches failed to reveal an obstruction or anything else which could account for the atelectasis. After the lungs were removed and sectioned the lower lobes were observed to be collapsed; the tissue was firm and practically airless, but the gross appearance was not quite that seen in organizing pneumonia. The remaining lobes were air containing and showed no gross evidence of tuberculosis, atelectasis or organizing pneumonia. The peribronchial lymph nodes were a little large, were firm and lay in somewhat fibrous mediastinal tissue.

The pericardial sac as observed from the outside was enlarged, suggesting that it contained a large heart, but when an attempt was made to open the pericardial sac there were found extensive, friable adhesions between the pericardium and the epicardium, which accounted readily for the enlargement of the pericardial sac. In places these adhesions were many millimeters thick, and everywhere they bound the pericardial and the epicardial surfaces together, obliterating entirely the pericardial cavity. After the heart was separated from these adhesions, it was obvious that it was not enlarged. Small grayish and translucent nodules were seen along the course of the small blood vessels in the epicardium. On

opening the cavities of the heart it became clear that the right auricle was small, that the tricuspid valve was delicate and normal and that the right ventricle showed nothing unusual, which was also true of the pulmonary conus and the valve leaflets. Likewise the left auricle with its appendage was rather small. The mitral valve, on the other hand, showed along its line of closure a few granular vegetations, all of which had smooth glistening surfaces. In one or two places these vegetations were reddened, but they had not the appearance of bacterial endocarditis. The aortic valve showed perhaps the most interesting and significant lesion found in the heart. In the endocardium covering the sinus aspect of the anterior leaflet there was a flat, spreading, granular vegetation with sharply outlined edges and a reddish color, extending over 3 to 4 mm. of the central portion of the valve surface. It did not extend to involve the filmy edge. In the anterior cusp, underlying the corpus arantii, was a thickening which was slightly yellowish, a change which is commonly found in these leaflets. Flat mural endocardial vegetations were not observed, nor were pocket lesions present. The myocardium, even though a little pale, was not the seat of any gross scarring and showed only a few distinct thick-walled blood vessels. The major coronary arteries were unobstructed. The aorta was free from arteriosclerotic change. The superior and inferior venae cavae were entirely normal in appearance.

The bony framework showed nothing more than a slight clubbing of the fingers.

Restrictions on the extent of the examination prohibited a study of the brain.

*Histologic Examination.*—The changes in the lungs are difficult to describe, but it is clear that they have been present for a long time. In the more consolidated areas it is almost impossible to say how the consolidation developed, i. e., whether the inflammatory cells first appeared in the interalveolar tissue and eventually encroached on the alveoli and collapsed them or whether the alveoli were the seat of the early changes. As the lung is observed in its present state there is a lobular consolidation, and the intervening air-containing alveoli are surrounded by thickened alveolar septums in which there is a low grade chronic inflammation. The inflammatory cells are almost universally of the mononuclear type; some are doubtless lymphocytes; a few are plasma cells, but the most characteristic, and, of course, most conspicuous, cell is a large mononuclear containing a deeply stained nucleus usually somewhat eccentrically placed and surrounded by a wide zone of slightly pinkish-staining cytoplasm (fig. 1). As the more consolidated areas are approached, this inflammatory reaction becomes more extensive and brings about a collapse of the alveoli. In these more affected areas, alveolar walls have disappeared and the lung tissue appears as a solid inflammatory mass in which the normal structural detail is completely lost, but in which the larger blood vessels are still identifiable. In some areas, in which the destruction is not so far advanced, hyaline plugs occur in the compressed alveoli. There are alveoli in which some polymorphonuclear leukocytes are embedded in a fibrin network which looks like a fresher pneumonia and is perhaps terminal. It is evident that this is not the ordinary type of organizing pneumonia with replacement of the collapsed lung by scar tissue. The greatly thickened pleural aspect of the lung is made up of a fibrous tissue which is highly vascular and still the seat of a fairly intense inflammation consisting almost entirely of mononuclear elements. A similar thickening and inflammation is present in the interlobar fissures.

In a section so prepared that a piece of lung and of pericardial wall is shown it becomes clear that the thickened pleural adhesions are much older and less intensely inflamed than those of the pericardium. The evidence for this is the

compact fibrous tissue with far fewer vascular channels in the pleural than in the pericardial adhesions. Likewise, the blood vessels in the thickened pleura have prominent walls and flattened endothelium, while those in the pericardial adhesions have delicate walls and prominent endothelium and their supporting stroma is more loosely arranged. In the pericardial adhesions there are also small foci of necrosis and hemorrhage. As one passes to another section showing the epicardium, it is observed that the adhesions over this surface are similar to those already described in the pericardium, that the mononuclear inflammatory reaction extends down to the myocardium and that in a few places mononuclear cells can be seen in the depth of the myocardium. They are usually confined to the perivascular tissue, but an exhaustive search fails to reveal a lesion or any cells which in the slightest manner resemble Aschoff bodies. In an occasional vessel there is a hyaline thrombus; this is apparently associated with some

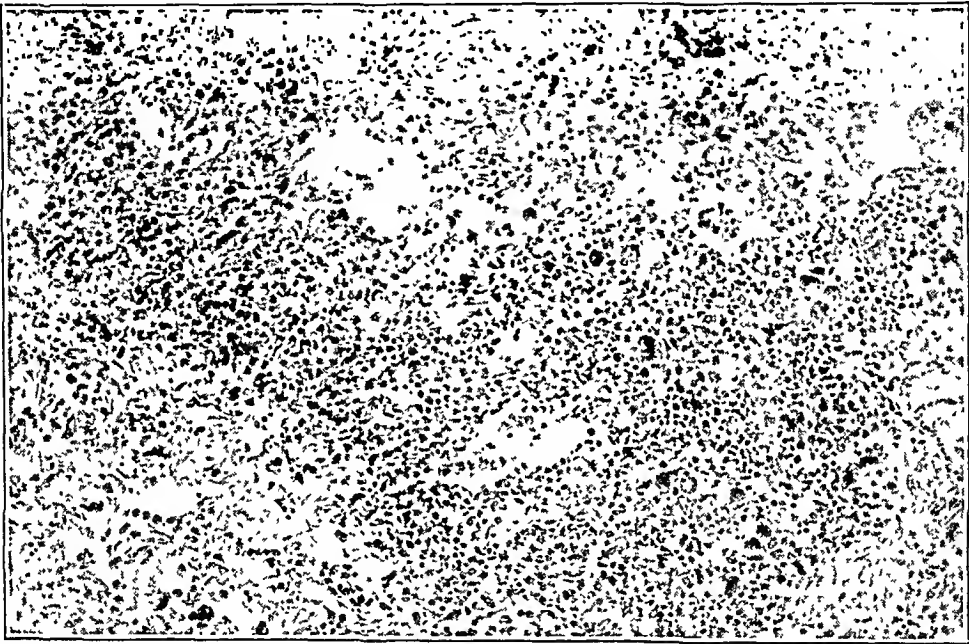


Fig. 1.—Inflammatory changes in the periphery of the lung adjacent to the pericardium.

necrosis of the vessel wall, but the change is certainly not that of periarteritis nodosa.<sup>9</sup> The myocardium itself seems well preserved; the muscular bundles and fibers are not hypertrophied, and no significant scarring is demonstrable.

The lesion on the sinus aspect of the aortic leaflet consists of an avascular thickening with a superficial infiltration of monocytes; near the midportion of this area is a small hyaline thrombus. At the edges of the thrombus the flattened endocardial lining seems to extend up onto the thrombus and then to become lost. One cannot be certain, but it rather appears that the endothelium originally covered this vegetation. There are no Aschoff bodies beneath the vegetation, and certainly there is none in the valve (fig. 2).

The gross lesions on the mitral valve when studied microscopically show little more than fibrous changes in which a few scattered mononuclear cells remain. There is no evidence of recent thrombi.

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9. Taylor, J. S., and Farley, D. L.: Periarteritis Nodosa: A Case Report with Necropsy, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* 3:15 (May) 1934.

In the liver there is a rather interesting distribution of fat-laden cells. At first it appears that the zone of cells surrounding the lobule and laden with fat are the periportal cells, but on careful observation it becomes clear that a narrow zone of liver cells is well preserved immediately around the portal area. And it is between this zone of cells and the central portion of the lobule that the deposition of fat has occurred. In no place could it be seen that the fat-laden cells have as yet become necrotic.

In the kidneys, the glomeruli appear large, the loops are not distinct and there is considerable intercapillary proliferation. At frequent intervals there are seen foci of necrosis in the glomerular tufts, which in not one single instance involve

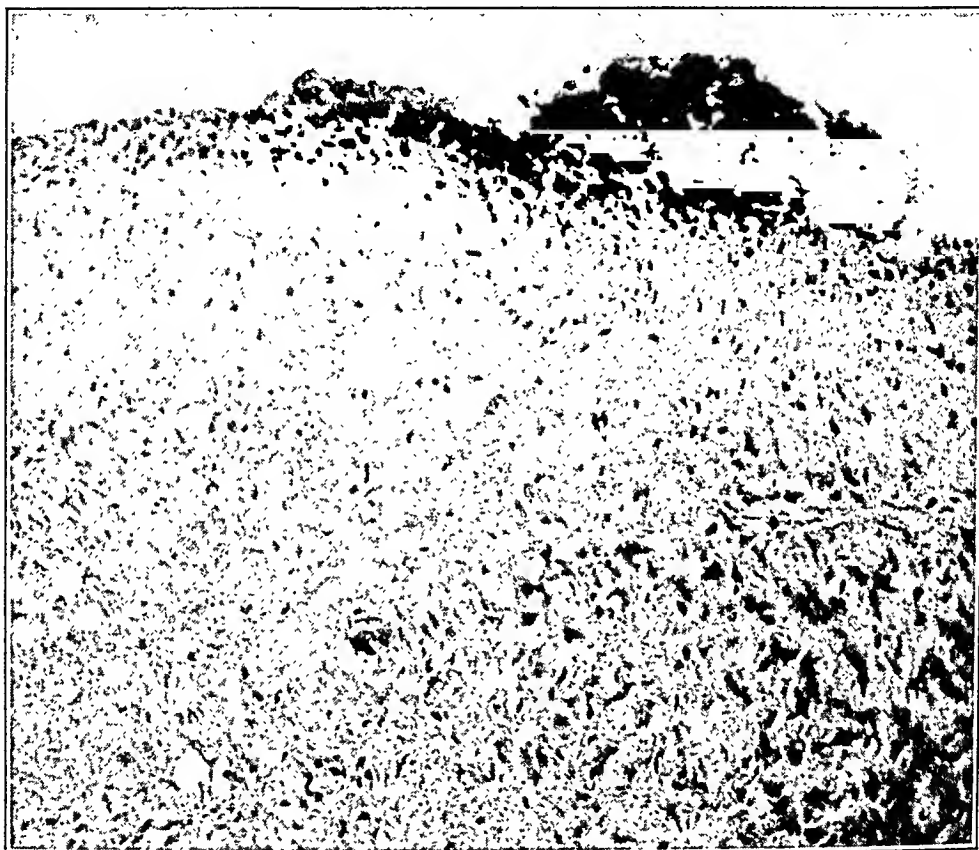


Fig. 2.—Vegetation on the aortic valve.

the entire glomerulus. Where the necrosis is not so far advanced, it appears that the vessel in the area is plugged by a hyaline thrombus. In the area of more advanced necrosis the nuclear material is broken up into small fragments, which still take a blue stain, and there are pinkish-staining colloid droplets. These necrotic zones seem clearly confined to individual loops of the capillary tuft, and in a few instances it seems that not even the entire loop is necrotic. Occasionally some portion of the glomerular tuft is adherent to the capsule, even in those glomeruli in which necrosis in the tuft is not demonstrable. Just outside of a few glomerular capsules are collections of mononuclear cells, some of which are fairly large and have an abundance of cytoplasm and a nuclear structure which resembles that of plasma cells. This inflammatory reaction is quite like that observed in the epicardium and many places in the lungs. The most

constant and striking observation in the kidneys is this mononuclear cell infiltration of the parenchyma just outside the glomerular capsule adjacent to the necrotic lesion in the tuft. There are no polymorphonuclear leukocytes, and in fact, little or no inflammation is present in these necrotic areas (fig. 3).

The spleen shows only prominent malpighian bodies and moderately thickened arterioles. In the pulp there are increased numbers of the large mononuclear cells characteristic of chronic splenic tumor.

The pancreas seems normal, as do the adrenals.

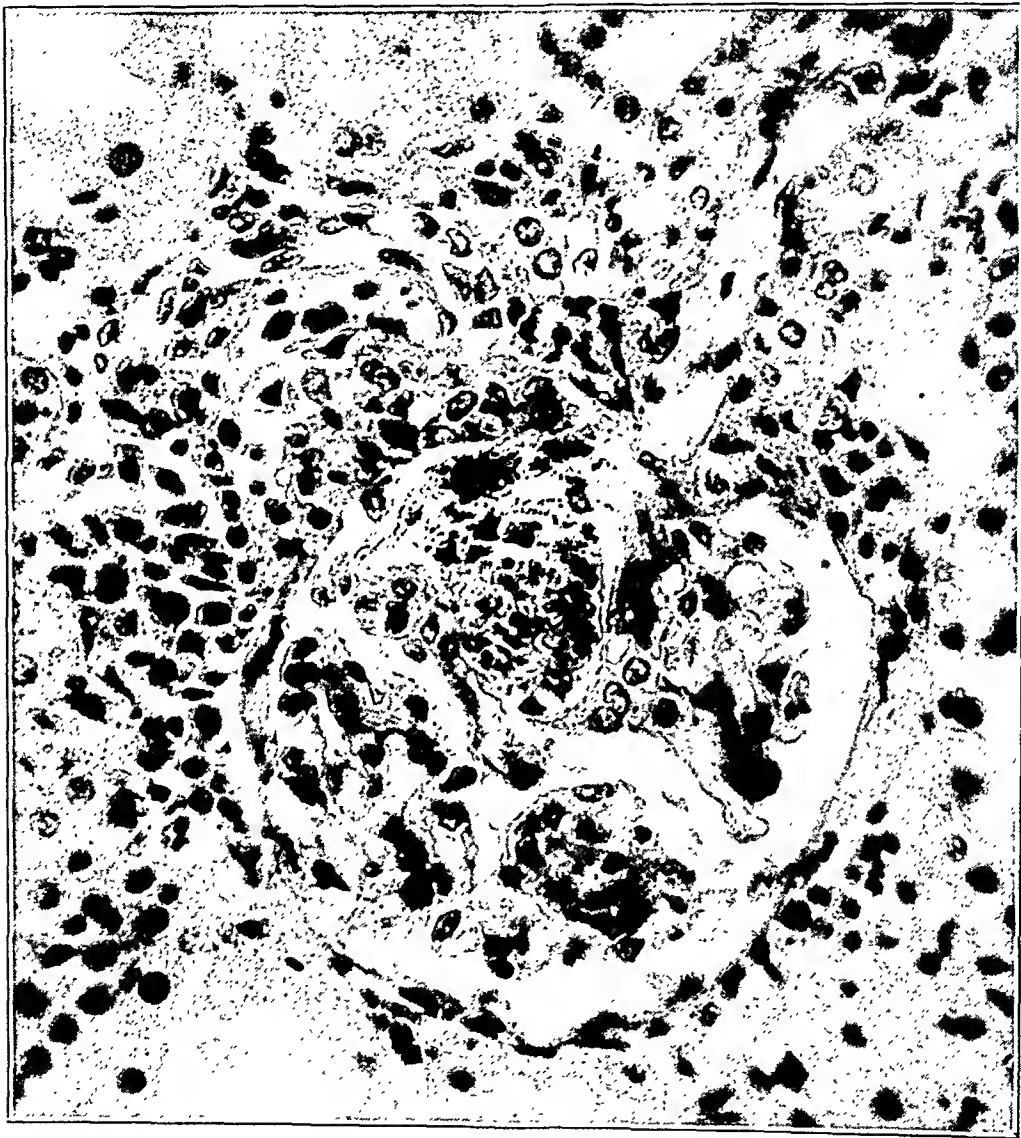


Fig. 3.—A necrotic lesion in a loop of a glomerular tuft, with accumulation of mononuclear cells in adjacent renal parenchyma outside of Bowman's capsule.

#### COMMENT

The clinical aspects of this case presented many symptoms and signs universally described in acute lupus erythematosus disseminatus, including prolonged fever, arthralgia, pleuritis, pericarditis, transient renal damage, leukocytopenia and persistently sterile blood cultures in a female

in the third decade of life. Thrombopenia and cutaneous lesions, including petechiae and purpura, were absent. An early presumptive diagnosis of acute lupus erythematosus disseminatus with atypical verrucous endocarditis was made, yet it was felt that the endocarditis per se did not contribute significantly to the clinical picture. The persistent signs of consolidation of the lungs were the most prominent and indeed most perplexing feature of the clinical course. These signs persisted from early in the course of the disease until death eight months later.

The accepted clinical picture of acute disseminated lupus erythematosus is usually accompanied by cutaneous lesions, which are not to be confused with the benign discoid butterfly eruption over the bridge of the nose and the malar prominences. It should be recalled that the rash of disseminated lupus erythematosus begins on the bridge of the nose as an impalpable reddish patch and may simulate for a short time the early stage of the local butterfly lesion. Before long this eruption becomes polymorphous and spreads over the face and ears and then to the skin of the neck, arms and thorax and indeed may be observed on practically any site of the cutaneous surface. On the other hand, Libman<sup>10</sup> has stated that the disease might occur without a cutaneous eruption and that the patient might have the general clinical picture of the disease for many months, with the eruption developing only a short time before death. Also, Baehr and associates, in reporting 23 cases of disseminated lupus erythematosus in which autopsy was done, mentioned that a similar clinical picture and somewhat similar vascular lesions in the kidneys and other viscera were observed in patients without cutaneous lesions. Yet, Rose and Pillsbury<sup>11</sup> expressed the belief that until the disease can be reproduced experimentally or until its cause is known, it seems unlikely that the existence of such a noneruptive form can be translated from a hypothesis into a fact. They believe, however, that the possibility of such an entity should be considered in a patient in whom no rash appears when fever, leukocytopenia, petechiae, purpura, embolic phenomena, arthralgia, evidence of endocarditis, pericarditis, renal injury, pleural effusion and persistently sterile blood cultures constitute the clinical picture. Still, with the present knowledge of acute disseminated lupus erythematosus the diagnosis is largely dependent on the presence of cutaneous lesions. And so, in the absence of cutaneous lesions a diagnosis of lupus erythematosus disseminatus is difficult to establish, even though most of the other signs of the disease are present.

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Just as it is difficult to establish the diagnosis on clinical grounds, so, too, is it difficult to make the diagnosis on postmortem examination. At necropsy the cutaneous lesion is the most 'constant single gross observation, but often fibrinous pericarditis, atypical verrucous endocarditis and polyserositis are also encountered. Histologically there may be evidence of diffuse endotheliitis described by Baehr and associates as (1) simple dilatation of capillary beds in certain areas, as in the skin, with extravasations of blood and serous fluid; (2) proliferative lesions of the endothelial lining of capillaries, arterioles and venules associated with thrombi which often occlude the lumen, and (3) degenerative and necrotizing lesions of the walls of such vessels with thrombosis and sometimes hemorrhage into the adjacent tissues. They expressed the opinion that the peculiar hyaline thickening of the capillary walls of the glomerular tufts, the so-called "wire loop lesion," is almost pathognomonic of acute disseminated lupus erythematosus. Others expressed the belief that this common distinct renal lesion does not exist (Stickney and Keith<sup>12</sup>), and it is true that in many fatal cases the patients do not show it (Mallory<sup>13</sup>). Atypical verrucous endocarditis now considered a part of this syndrome has been adequately described by Libman and Sacks, and later by Gross,<sup>14</sup> and in equivocal cases the endocardial lesion can be differentiated from rheumatic endocarditis by absence of Aschoff bodies in the myocardium. Curiously enough, in these cases in which there is endocardial and pericardial involvement the myocardium is usually spared, and cardiac hypertrophy is rare. Yet in many cases the heart is entirely free from any endocardial involvement. Clearcut pulmonary lesions have not been described. Indeed, we are compelled to conclude that there is no single pathognomonic visceral lesion, and in doubtful cases the diagnosis seems tenable only by coordination of the clinical and the pathologic aspects.

Our patient exhibited many of the critical manifestations of lupus erythematosus disseminatus, namely, prolonged clinical course with fever, sterile blood cultures, leukocytopenia, endocarditis, arthralgia, adhesive pericarditis with polyserositis and glomerular lesions. In addition, there were noted long-continued signs of consolidation in the lungs caused by the pulmonary changes already described. The glomerular

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lesions present were not of the wire loop pattern, but the specificity of the latter is doubted. The valve lesions did not resemble those usually observed in atypical verrucous endocarditis, but certainly were not those encountered in rheumatic fever or in bacterial endocarditis. Absence of a characteristic eruption was the chief obstacle in establishing a diagnosis of lupus erythematosus disseminatus in our case, and yet the abundance of the other clinical and pathologic features points strongly to this disease. It may be justifiably concluded that in a case of a disease with such a variable picture, even at autopsy, the lack of one frequent sign should not preclude a diagnosis of that disorder.

#### SUMMARY

A consideration of the complex clinical manifestations of lupus erythematosus disseminatus is combined with the report of a case in which the patient exhibited pronounced pulmonary signs and lesions but showed no cutaneous eruptions at any time.

# URIC ACID PARTITION IN GOUT AND IN HEPATIC DISEASE

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The problem of solubility of uric acid and urates in body fluids has been the subject of extensive studies. Uric acid is weak and dissolves in water in small amounts only. Sodium urate is more easily soluble,<sup>1</sup> but its solubility is depressed by the addition of sodium chloride. A physiologic solution of sodium chloride dissolves only one tenth of the amount soluble in distilled water.<sup>2</sup> The solubility of sodium urate in body fluids is much higher, however, than the determination of its solubility in physiologic solution of sodium chloride would suggest. Schade and Boden<sup>3</sup> observed that sodium urate solutions were characterized by properties specific for colloidal solutions, such as opalescence, gel formation and the Tyndall phenomenon (see also Bechhold and Ziegler<sup>4</sup>). This suggested the existence of a colloidal form of uric acid in body fluids (compare, however, Hoeber<sup>5</sup>). Freundlich and Farmer-Loeb<sup>6</sup> examined the electrical conductivity of sodium urate solutions and noted the presence of sodium ions, urate ions, undissociated noncolloidal sodium urate, colloidal neutral urate and colloidal urate ions. All these constituents of the sodium urate solution are in a state of equilibrium, which may vary according to concentration, acidity, temperature, etc.

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From the Medical Services, the Nutrition Clinic, the Department of Chemistry Laboratories of Mount Sinai Hospital.

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The recognition of the colloidal properties of uric acid solutions offered to the clinician plausible explanations for various clinical observations, particularly in regard to the excretion of uric acid, gout and the formation of uric acid calculi.

Regardless of certain controversies about the colloidal state of uric acid in body fluids, clinical observations led years ago to the assumption of "free" and "bound" uric acid. To the best of our knowledge, it was Minkowski<sup>7</sup> who first postulated the existence of combined uric acid in blood; on the basis of further experimental evidence, he reiterated his opinion more than thirty years later, in his last review of the subject.<sup>8</sup> Benedict and his co-workers<sup>9</sup> succeeded in isolating from the blood of various species of animals and from human blood a compound of one molecule of uric acid with one molecule of dextrorotatory ribose. It was assumed that this substance derives either from inosinic acid by oxidation of the hypoxanthine component or from guanylic acid by oxidation of the guanine moiety. According to Peters and Van Slyke,<sup>10</sup> this is the only organic combination of uric acid in the animal body the existence of which has been definitely proved (compare also Bornstein and Griesbach<sup>11</sup>). Fischer and Helferich, cited by Minkowski,<sup>8</sup> expressed a belief in the existence in the organism of an easily hydrolyzable nucleoside of uric acid, the presence of which is difficult to demonstrate.

A few French authors attempted to differentiate free uric acid from combined uric acid. Guillaumin<sup>12</sup> determined the amount of free uric acid in the blood after preliminary precipitation as a silver salt and the total uric acid directly by the Folin method in the metaphosphoric acid filtrate. Chabanier, Lebert and Lobo-Onell,<sup>13</sup> employing compensatory dialysis, concluded that all uric acid in the blood was free, as it was

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entirely dialyzable. Delaville and Jones<sup>14</sup> were the first to use ultrafiltration; they determined the amount of free and of total uric acid in the serum by ultrafiltration before and after hydrolysis with 3 per cent sulfuric acid. Without giving details of their method, they reported for the serum of normal persons 70 per cent free and 30 per cent combined uric acid; in a single patient with gout and in a single patient with cirrhosis of the liver a reversal of this ratio was observed. Achard, Levy and Marinowski<sup>15</sup> compared the results of ultrafiltration with those of precipitation by trichloroacetic acid; in their brief communication they presented conclusions similar to those of Delaville and Jones. Khouri,<sup>16</sup> attacking this problem from a slightly different viewpoint, subjected the serum to hydrolysis with tenth-normal sulfuric acid before and after precipitation of the proteins with trichloroacetic acid; this method did not yield constant values for the free and the combined uric acid.

Von Przylecki, Grynberg and Szrajber<sup>17</sup> studied the combination of uric acid with proteins, such as casein, gelatin, albumin and globulin, by varying the acidity, the concentration of uric acid, etc. The combination of uric acid with these proteins was reversible, with dissociation prevailing in the sol state and combination in the gel state. The reversibility also depended on the nature of the proteins. Addition of such electrolytes as sodium chloride and magnesium chloride led to dissociation. According to these authors, uric acid may occur in the body fluids in three states: molecularly disperse, colloiddally disperse and bound to proteins. An equilibrium exists among these three states depending on the colloidal state of the protein, the degree of dispersion and the presence of electrolytes. In another study, Grynberg and Kisiel<sup>18</sup> performed similar experiments with various fats and lipoids; there was no binding of uric acid with these substances at  $p_H$  7.5 to 8.5. Bennhold<sup>19</sup> employed the method of electrocataphoresis for the study

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14. Delaville, M., and Jones, M. C.: Le dosage de l'acide urique dans le plasma sanguin, *Compt. rend. Soc. de biol.* **92**:522, 1925. Jones, M. C.: Le taux de l'acide urique dans le plasma sanguin du sujet normal. Rapport entre l'acide urique libre et total, *ibid.* **93**:295, 1925.

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of free and of bound uric acid. From his experiments he concluded that uric acid in the blood is partly free and partly loosely bound to albumin and that an equilibrium exists between these two fractions. With diminishing concentration of free uric acid, the bound uric acid is set free.

The question as to the colloidal and the bound state of uric acid in serum has not been settled by studies of uric acid clearance. Brøchner-Mortensen<sup>20</sup> expressed the belief that uric acid in the blood does not exist in a colloidal or combined form but that it is a true threshold substance, completely excreted by the glomeruli and probably partly reabsorbed by the tubules. Berglund and Frisk,<sup>21</sup> however, assumed that part of the uric acid is in a nonfiltrable form, that only the free uric acid passes the kidney and that no reabsorption from the filtrate occurs. An important point in all these considerations is the dialyzability and ultrafiltrability of the uric acid in blood. However, dialysis and ultrafiltration represent materially different procedures, and each of them is apt to solve different problems (see section on dialysis studies).

Only the following reports on the behavior of uric acid during ultrafiltration of blood could be found. The exact procedure is not described in any of them, and altogether only a few normal subjects and a few subjects with a pathologic condition have been investigated. The results of Delaville and Jones<sup>14</sup> and of Achard, Levy and Marinowski<sup>15</sup> have just been referred to. In a recent paper, Lambie<sup>22</sup> presented a study of a single case of juvenile gout of obscure origin; ultrafiltration of the patient's serum revealed that only 28 to 37 per cent of the uric acid of the plasma was filtrable; however, after splenectomy 63 to 100 per cent of the uric acid could be recovered in the ultrafiltrate. The ultrafiltration was performed with a collodion membrane of unknown pore size. In 3 normal subjects used for comparison bound uric acid was not found.

In view of the lack of reliable data, we decided to study the partition of uric acid under normal and under pathologic conditions. After a series of experiments with dialysis, ultrafiltration was used exclusively in the studies reported here. This report deals first with the observations on normal subjects and subsequently with those on subjects with pathologic conditions, particularly gout and hepatic disease.

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20. Brøchner-Mortensen, K.: On Variations in the Uric Acid Clearance After Administration of Purine, with Special Reference to the Threshold Protein, *Acta med. Scandinav.* **99**:525-539, 1939.

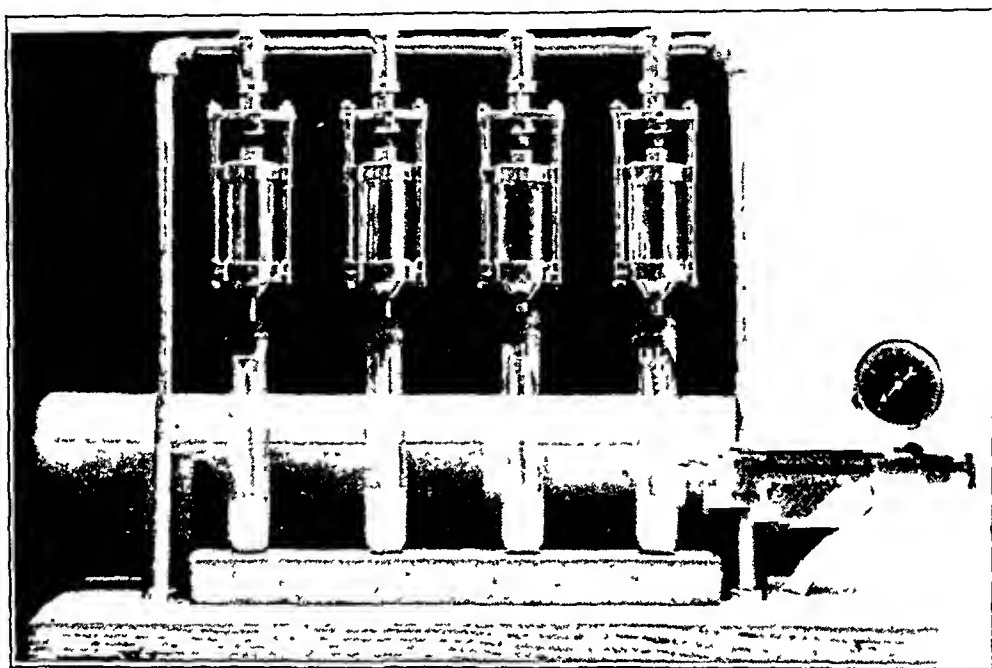
21. Berglund, H., and Frisk, A. R.: Uric Acid Elimination in Man, *Acta med. Scandinav.* **86**:233-267, 1935.

22. Lambie, C. G.: A Study of Juvenile Gout in a Patient Suffering from Chronic Erythronoclastic Anemia of Obscure Origin, Together with Observations upon Physical States of Uric Acid in Blood and Effects of Splenectomy, *M. J. Australia* **1**:535-558, 1940.

## METHOD

The uric acid content of the blood serum was determined by the method of Benedict with the modification of Brown.<sup>23</sup> The blood proteins were removed by precipitation with tungstic acid. We agree with Jacobson<sup>24</sup> and others that the determination of uric acid in serum is preferable to that in whole blood.

The partition of uric acid was studied by ultrafiltration. In the tables the figures for free uric acid signify the acid in the ultrafiltrate, whereas those for bound uric acid represent the difference between the uric acid content of the tungstic acid filtrate (total uric acid) and the free uric acid. The following method of ultrafiltration was employed: Fresh serum was filtered through a "600" cellophane membrane at a pressure of 80 pounds (36 Kg.) of nitrogen per square inch (6 sq. cm.). The apparatus used was designed and built by Mr. J. Vondrak, of these laboratories (figure). We found it imperative to work under uniform condi-



Apparatus for the ultrafiltration of serum. Circular filters consisting of cellophane disks resting on metal sieve plates are situated at the bottom of four hermetically sealed heavy glass cylinders (inside diameter 29 mm.). The pressure is supplied from the tank of nitrogen conveniently placed in a horizontal position behind the cylinders. The arm leading from the tank to the manifold is supplied with a needle valve and a pressure gage. The filtrate drips into the graduated conical 15 cc. centrifuge tubes, which are held in position in the loosely stoppered 50 cc. centrifuge tubes. A case with heavy wired glass, fitting over the manifold and the four ultrafilters, is omitted in the photograph.

tions as far as the following factors were concerned: (a) duration of filtration, (b) amount of serum and of filtrate used and (c) handling of filtrate.

(a) To evaluate the time factor, specimens of the same sample of serum were filtered seven to sixty-five hours. The filtrates obtained in the course of seven to twenty-four hours showed practically identical composition, whereas filtrates

23. Brown, H.: Uric Acid in Blood, *J. Biol. Chem.* **68**:123-133, 1926.

24. Jacobson, B. M.: The Uric Acid in the Serum of Gouty and Non-Gouty Individuals, *Ann. Int. Med.* **11**:1277, 1938.

obtained after twenty-six to sixty-five hours varied considerably in uric acid content, for reasons not definitely determined. On the basis of these tests, all ultrafiltrations were carried out for eighteen to twenty-four hours. During this time an amount sufficient for uric acid analysis in duplicate is obtained.

(b) The smallest possible amount of serum had to be used because in some of these investigations a sample of blood had to be taken daily from the same subject, and in some instances, several times in the course of one day. Four cubic centimeters of serum proved sufficient to yield 1.5 cc. of ultrafiltrate within eighteen to twenty-four hours.

(c) The ultrafiltrate obtained under the aforementioned conditions is a slightly cloudy and turbid fluid. A series of tests was performed to determine the nature of the cloudiness and the influence of this factor on uric acid analysis. Biuret

TABLE 1.—*Effect of Centrifuging on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Supernatant Fluid	Sediment
401.....	5.6	2.9	5.2
402.....	4.3	2.3	4.1
403.....	5.5	3.1	4.8

TABLE 2.—*Effect of the Addition of Chloroform on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Without Chloroform	With Chloroform
404.....	4.7	4.2	4.0
405.....	5.5	4.8	4.4
406.....	5.7	4.4	4.1
Mixed serum.....	5.9	4.8	4.7

and sulfosalicylic acid reactions of the filtrate were negative. Microscopic examination revealed numerous saprophytic bacteria as cause of the turbidity. It was possible to centrifuge them off and thus to obtain a clear supernatant fluid. However, the uric acid content of this supernatant fluid was considerably lower than that of the residue. Table 1 illustrates the results of centrifugation. It is therefore imperative to avoid centrifuging and, on the contrary, to stir up the ultrafiltrate, thus providing equal distribution of the uric acid.

In a group of experiments we tried to prevent the growth of bacteria in the ultrafiltrates and compared the uric acid content of sterile ultrafiltrates and that of unsterile controls of the same sample of serum. The first series was performed with the addition of 1 to 2 drops of chloroform to the ultrafiltrate. The chloroform had no effect whatsoever on the growth of bacteria, but there was a small decrease of uric acid content in the chloroform-containing specimens (table 2). Instead of using other disinfectants to prevent bacterial growth, we examined a series of serums under sterile conditions. The sterility was tested at every step of the procedure. The sterile ultrafiltrates were water clear and showed no sediment after centrifuging. The nonsterile ones appeared mildly cloudy, as just

described. This proved that the cloudiness of the ultrafiltrates is due to bacterial growth and can be prevented by sterile handling. It is evident from the results summarized in table 3 that the nonsterile controls contained the same amounts of uric acid as the sterile ultrafiltrates, provided the former were not centrifuged prior to analysis.

The presence of bacteria in the ultrafiltrate does not interfere with the determination of uric acid. Precautions for maintaining strict sterility may thus be omitted as superfluous, besides being time-consuming and injurious to the permeability of the membranes.

#### DIALYSIS STUDIES

Three samples of serum, with a uric acid content varying from 3.7 to 8.4 mg. per hundred cubic centimeters, were dialyzed in cellophane bags<sup>25</sup> from two to four days against running tap water. Lithium urate was added in varying amounts to a specimen of each sample, raising the uric acid content before dialysis to 10.7, 14.0 and 24.5 mg. per hundred

TABLE 3.—*Effect of Sterilization on the Uric Acid Content of Ultrafiltrates of Human Serum*

Subject No.	Total Uric Acid, Mg./100 Cc.	Uric Acid in the Ultrafiltrate, Mg./100 Cc.	
		Nonsterile	Sterile
407.....	2.9	2.4	2.4
408.....	4.3	3.6	3.7
409.....	5.2	5.0	4.9
Mixed serum.....	5.8	5.3	5.3

cubic centimeters. After dialysis, no uric acid was found in the original samples or in the specimens in which the uric acid had been increased.

In a separate experiment a normal subject received 480 mg. of uric acid by intravenous injection; specimens of blood were drawn before the injection and one-half hour and three, six and twenty-four hours afterward. The uric acid content rose from 4.3 to 8.0 mg. per hundred cubic centimeters half an hour after the injection and gradually dropped to 6.7, 6.0 and 5.0 mg. per hundred cubic centimeters, respectively, in the subsequent specimens. In all five specimens the uric acid was completely removed on dialysis, or traces of less than 0.04 mg. per hundred cubic centimeters remained after twenty-four hours.

It was mentioned in a preceding paragraph that the equilibrium between free and combined uric acid is labile and can easily be disturbed by various factors, e. g., dialysis. Apparently, dialysis removes first the available free uric acid. This disturbs the equilibrium, and more uric acid is liberated, becomes dialyzable and is removed in turn from the

25. Visking sausage casing.



serum. Hence, dialysis is not suitable for the study of uric acid partition in protein-containing fluids (compare the statement of Freundlich and Farmer-Loeb <sup>6</sup>).

#### URIC ACID PARTITION IN NORMAL HUMAN SERUM

The range of the total uric acid and the ultrafiltrable and the non-ultrafiltrable fractions was established by a series of determinations on

TABLE 4.—*Uric Acid Partition in Normal Subjects*

Subject No.	Condition	Date	Total Uric Acid, Mg./100 Cc.	Uric Acid Partition		Bound Uric Acid, Percentage of Total Uric Acid
				Filtrable, Mg./100 Cc.	Non-filtrable, Mg./100 Cc.	
1	Duodenal ulcer.....	2/20/41	4.2	3.8	0.4	9
		2/25/41	4.0	3.3	0.7	18
		3/ 1/41	4.8	3.8	1.0	21
2	Old coronary artery occlusion..	2/18/41	6.1	5.3	0.8	13
		2/21/41	6.8	5.5	1.3	19
		2/26/41	5.2	4.3	0.9	17
3	Congenital heart disease.....	2/17/41	3.4	2.8	0.6	18
		2/20/41	2.6	2.2	0.4	15
		2/25/41	3.0	2.5	0.5	17
4	Duodenal ulcer.....	2/18/41	4.1	3.3	0.8	19
		2/21/41	6.2	5.2	1.0	16
5	Normal.....	9/ 9/40	5.7	4.4	1.3	23
		1/13/41	5.2	4.1	1.1	21
6	Normal.....	9/13/40	5.1	3.9	1.2	24
		3/ 1/41	4.0	3.2	0.8	20
7	Obesity.....	3/ 5/41	5.2	4.2	1.0	19
		3/19/41	5.0	3.9	1.1	22
8	Duodenal ulcer.....	9/ 8/40	4.8	4.4	0.4	8
9	Thromboangiitis obliterans.....	9/ 8/40	6.1	5.1	1.0	16
10	Postural hypotension.....	9/ 8/40	6.6	5.8	0.8	12
11	Typhus (Brill's disease).....	9/ 9/40	5.3	4.4	0.9	17
12	Normal.....	9/ 8/40	5.6	5.0	0.6	11
13	Angina pectoris.....	9/ 9/40	6.0	4.9	1.1	18
14	Arteriosclerotic heart disease...	9/15/40	4.7	4.2	0.5	11
15	Sinusitis.....	9/15/40	5.5	4.8	0.7	13
16	Arteriosclerotic heart disease...	9/18/40	5.7	4.4	1.3	23
17	Jejunal ulcer.....	9/24/40	4.5	3.6	0.9	20
18	Convalescence from pneumonia	10/29/40	4.3	3.6	0.7	16
19	Peptic ulcer.....	11/ 5/40	5.2	5.0	0.2	4
20	Abortion.....	11/ 8/40	3.4	3.1	0.3	9
21	Scleroderma.....	12/18/40	6.8	5.8	1.0	15
22	Obesity.....	3/ 5/41	4.6	3.7	0.9	20
Average.....			5.0	4.2	0.8	16

normal subjects. These consisted of 3 healthy volunteers and of patients convalescing from various diseases who were free of clinical symptoms. A few suffered from chronic conditions, such as peptic ulcer, obesity and compensated heart disease. Six of a total of 22 subjects were tested a second time after the experiments recorded in table 4, and in turn, 3 of these 6 were tested a third time.

The uric acid content of the serum varies from 2.6 to 6.8 mg. per hundred cubic centimeters. Compared with a series of one hundred

determinations by Jacobson<sup>21</sup> of uric acid in serum the lowest values in the present series are moderately higher than the lowest figures reported by this author (1.8 mg. per hundred cubic centimeters), but the upper limit is practically the same in both series. The average recorded by Jacobson was 4.2 per hundred cubic centimeters, compared to 5.0 mg. per hundred cubic centimeters obtained in the present investigation.

The ultrafiltrable fraction of the serum uric acid ranges from 2.2 to 5.8 mg. per hundred cubic centimeters, with an average of 4.2 mg. The nonfiltrable bound uric acid ranges from 0.2 to 1.3 mg. per hundred cubic centimeters, with an average of 0.8 mg. Expressed in percentage of the total uric acid, the bound uric acid averages 16 in normal subjects, with a range from 4 to 24.

Only in subject 1 the bound uric acid ranged from 9 to 21 per cent. The percentage of bound uric acid varied less even in much longer periods in the other subjects, for instance, from 13 to 19 in subject 2 and from 20 to 24 in subject 6. The uric acid partition is apparently stable in the serum of a given person.

#### URIC ACID PARTITION IN PATIENTS WITH MISCELLANEOUS PATHOLOGIC CONDITIONS

The uric acid partition in patients with various pathologic conditions was subsequently examined. We were guided by two viewpoints in the selection of subjects: First, we wished to survey all important disease groups, such as pulmonary, cardiovascular, renal and hepatic diseases and diseases of the blood, and second, we were interested in conditions known to be associated with disturbance of the purine metabolism, such as gout, uremia and forms of leukemia. It soon became evident that hepatic disease and gout may produce an anomalous picture. Hence, larger groups of patients with these diseases were examined and will be discussed in subsequent sections.

Table 5 presents the results of study of these patients with the exception of those with gout and hepatic disease. Normal values for total, as well as for bound, uric acid were encountered in the following patients: 101, with acute cellulitis of the leg; 102, with typical allergic bronchial asthma, and 108, with nephrotic hypoproteinemia, with total protein values varying from 3.4 to 5.2 Gm. per hundred cubic centimeters and inversion of the albumin-globulin ratio. Four persons with diabetes, (patients 114 to 117), 1 with ketosis, showed no abnormalities except a slightly elevated bound uric acid ratio of 26 per cent in patient 116.

In the following conditions elevated values for total uric acid were associated with a normal partition: uremia with marked azotemia

(patients 106 and 107), lymphatic leukemia (patients 118, 119 and 120), myeloid leukemia (patient 121), myasthenia gravis (patient 125) and amyotrophic lateral sclerosis (patients 122, 123 and 124).

The serum uric acid in patients with exophthalmic goiter behaved normally except in a patient suffering from a peculiar form of persistent

TABLE 5.—*Uric Acid Partition in Patients with Miscellaneous Pathologic Conditions Other Than Hepatic Disease or Gout*

Subject No.	Condition	Date	Total Uric Acid, Mg./100 Cc.	Uric Acid Partition		Bound Uric Acid, Percentage of Total Uric Acid
				Filtrable, Mg./100 Cc.	Non-filtrable, Mg./100 Cc.	
101	Cellulitis of leg.....	10/29/40	4.8	4.3	0.5	10
102	Bronchial asthma.....	10/29/40	2.9	2.4	0.5	17
103	Bronchiectasis.....	11/12/40	7.2	5.5	1.7	24
104	Acute coronary artery occlusion	10/29/40	7.4	7.0	0.4	5
105	Pyloric obstruction.....	1/ 3/41	4.6	3.7	0.9	20
106	Uremia.....	11/17/40	8.0	7.1	0.9	11
107	Uremia.....	11/17/40	15.6	14.9	0.7	5
108	Nephrosis; hypoproteinemia....	11/12/40	4.4	4.0	0.4	9
109	Persistent hyperthyroidism....	11/24/40	5.1	2.6	2.5	49
		11/26/40	5.1	4.5	0.6	12
110	Exophthalmic goiter.....	11/27/40	6.6	5.6	1.0	15
111	Exophthalmic goiter.....	12/ 8/40	5.5	4.4	1.1	20
112	Exophthalmic goiter.....	12/ 8/40	3.3	2.8	0.5	15
113	Exophthalmic goiter.....	12/25/40	6.2	5.4	0.8	13
114	Diabetes.....	11/ 8/40	2.8	2.2	0.6	21
115	Diabetes.....	11/ 8/40	3.3	2.9	0.4	12
116	Diabetes.....	12/ 1/40	5.3	3.9	1.4	26
117	Diabetes; ketosis.....	12/18/40	4.4	3.9	0.5	11
118	Lymphatic leukemia.....	12/ 2/40	5.7	4.9	0.8	14
119	Lymphatic leukemia.....	12/ 8/40	5.6	4.6	1.0	18
120	Lymphatic leukemia.....	12/25/40	3.1	2.4	0.7	23
121	Myeloid leukemia.....	12/ 2/40	7.2	5.7	1.5	20
122	Amyotrophic lateral sclerosis...	11/10/40	8.0	7.2	0.8	10
123	Amyotrophic lateral sclerosis...	11/10/40	10.5	8.4	2.1	20
124	Amyotrophic lateral sclerosis...	11/10/40	10.5	8.5	2.0	19
125	Myasthenia gravis.....	11/10/40	6.9	6.2	0.7	10
126	Multiple myeloma.....	11/14/40	9.8	6.3	3.5	36
		11/24/40	8.6	5.4	3.2	37
127	Multiple myeloma.....	4/ 9/41	6.1	5.5	0.6	10

hyperthyroidism or possibly a hypothalamic lesion, who exhibited active symptoms of the disease in association with unusual muscular disturbances. Because of its peculiarities, a short abstract of the history will follow.

B. M., a 29 year old man, had an episode of polydipsia, diarrhea, a gain of 100 pounds (45 Kg.) within six months and dropping of the left eyelid eight years prior to admission. A year and a half before he followed a strict diet, with a loss of 100 pounds in six months. Toward the end of this period he displayed symptoms of hypermetabolism, and his basal metabolic rate was +60 per cent.

After the administration of compound solution of iodine U. S. P. his basal metabolic rate decreased to +30 per cent. A subtotal thyroidectomy was performed. One month after operation symptoms recurred, with weakness, tachycardia and sweating. For the past year and a half he had had attacks of intermittent paralysis of the upper and lower extremities lasting eight to ten hours. On occasion these were accompanied by nausea, vomiting, diarrhea and incontinence.

On physical examination he appeared well nourished and overactive. Ptosis of the left eyelid, slight exophthalmos, lidlag and stare were present. The blood pressure was 140 systolic and 80 diastolic. There was slight nystagmus on looking to the left.

Laboratory examination yielded the following data: The blood urea nitrogen was 10 mg. per hundred cubic centimeters; the total cholesterol in the blood, 155 mg. per hundred cubic centimeters; the esterified cholesterol, 55 mg. per hundred cubic centimeters; the result of the galactose tolerance test, 1.1 Gm.; the Wassermann reaction, negative, and the basal metabolic rate, +43 and +52 per cent.

Inasmuch as thyroidectomy had been almost complete and there was no evidence of any substernal extension of the thyroid, it was believed that the hypermetabolism was not due to hyperthyroidism but possibly to hypothalamic lesion following encephalitis.

In contrast, 4 other patients with exophthalmic goiter, with and without medication with iodine, showed a normal uric acid picture.

The next to the last patient in table 5 (patient 126) had values which showed marked deviation from the normal figures both for total and for bound uric acid. A summary of his history follows:

A 46 year old man had multiple myeloma with loss of weight, pallor and bleeding from the gums for four weeks prior to admission. The liver and the spleen were enlarged. There was marked secondary anemia, with 2,100,000 red cells per cubic millimeter and a hemoglobin concentration of 23 per cent; Bence Jones protein was found in the urine. Typical bone changes were observed on roentgen examination.

The serum of this patient was of syrup-like appearance and of abnormally high viscosity. The total protein content rose gradually from 7.4 to 11.6 Gm. per hundred cubic centimeters, with 3.2 Gm. of albumin and 8.4 Gm. of globulin. The total uric acid content was 8.6 to 9.8 mg. per hundred cubic centimeters, the bound uric acid ratio on two occasions being 36 and 37 per cent, respectively. A second person (patient 127) with this disease but without hyperproteinemia displayed a normal uric acid picture.

The uric acid partition does not deviate from that of normal persons, with the exception of values for the aforementioned patients with atypical exophthalmic goiter and with multiple myeloma, the significance of which will be discussed later. The total uric acid in the serum is elevated in patients with uremia and amyotrophic lateral sclerosis, resulting in a comparatively high average value for the entire group given in table 5,

namely, 6.2 mg. per hundred cubic centimeters. The bound uric acid ratio averages 15 per cent of the total uric acid, which coincides with the value given for normal uric acid partition.

#### URIC ACID PARTITION IN PATIENTS WITH HEPATIC DISEASE

Changes of uric acid metabolism have frequently been reported in patients with hepatic disease. Robecchi and Muttini<sup>26</sup> reported low values for uric acid in the blood of patients with hepatic disease and a return to normal figures on clinical improvement. They also observed retarded elimination and a delayed "uric acid curve" in serum after intravenous injection of this substance. Similar observations were made on patients with gout. On the other hand, Chrometzka<sup>27</sup> reported high figures for uric acid in patients with hepatitis. Brøchner-Mortensen<sup>28</sup> found increased values for uric acid in the blood of patients with disease of the liver and the biliary system. In those with the severest hepatic damage, hyperuricemia did not occur. In spite of a few contradictory findings, one gains the impression that obstructive jaundice leads to an elevation of uric acid content but that hepatic damage, at least in severe degrees, leads to low values. In the present series, a low titer of uric acid in the blood was met with only in patients with icterus of long duration and possible secondary hepatic damage (carcinoma of the pancreas, cholangitis with pylephlebitis). Patients with hepatitis and cirrhosis of the liver presented no consistent change in the total uric acid content of the blood.

The present group, summarized in table 6, consists of 28 patients with hepatic disease, namely, 8 with toxic hepatitis, 10 with cirrhosis of the liver, 3 with carcinoma of the head of the pancreas with obstructive jaundice and 1 each with cholangitis, biliary cirrhosis, carcinoma of the gallbladder, cholelithiasis with superimposed toxic hepatitis, cholelithiasis complicated by suppurative cholangitis and pylephlebitis, lymphatic leukemia and metastatic carcinoma superimposed on cirrhosis of the liver.

In the largest subgroup, represented by cirrhosis of the liver, the total content of uric acid varies from 2.9 to 7.5 mg. per hundred cubic centimeters (patients 208 to 217). The average of 4.6 mg. per hundred cubic centimeters is comparable with the normal average of 5.0 mg. The uric acid partition in the first 5 patients (208 to 212), having values for bound uric acid ranging from 8 to 24 per cent of the total uric acid,

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26. Robecchi, A., and Muttini, C.: Studi sul metabolismo purinico; il ricambio purinico negli epato-pazienti, *Arch per le sc. med.* **65**:475-510, 1938.

27. Chrometzka, F.: Die zentrale Stellung der Leber im Purinstoffwechsel und ihre Bedeutung fuer die Pathogenese der Gicht, *Klin. Wchnschr.* **51**:1877, 1936.

28. Brøchner-Mortensen, K.: The Uric Acid in Blood and Urine in Health and Disease, *Medicine* **19**:161-229, 1940.

may be considered normal. The values for the other 5 patients, 213 to 217, differ from the normal picture by at least one bound uric acid ratio above 24 per cent during repeated examinations. All these patients show in the course of their illness normal figures changing into abnormal ones or vice versa. Thus, the value of 27 per cent bound uric acid in patient 213 decreased to 7 per cent within one week; the change was accompanied by clinical improvement, probably due to extensive therapy. In contrast, patient 215, starting with a normal uric acid partition, showed an elevation of the bound uric acid ratio during progressive deterioration of the general condition, which led to a fatal outcome. It is impossible to decide on the basis of the present observations why patients with cirrhosis may in some instances present these transient changes of uric acid partition. One has to consider that the patients with normal uric acid partition have been examined only once, with 1 exception, so that a temporary deviation of the uric acid partition could easily have been missed. It is plausible that these fluctuations are connected with episodes of acute exacerbation in the course of the disease.

In the subgroup of 8 patients with toxic hepatitis the total uric acid content ranges between 2.6 and 6.2 mg. per hundred cubic centimeters, averaging 4.7 mg., a normal value. In 5 persons (patients 222, 223, 224, 227 and 228) the uric acid partition is entirely normal, with bound uric acid ratios between 11 and 21 per cent. Four of these patients have been examined during improvement of the general condition and subsiding icterus. The fifth one (patient 227) had long-lasting but mild hepatitis. In the other 3 persons (patients 221, 225 and 226) normal values for total uric acid are associated with abnormal uric acid partition, up to 41 per cent bound uric acid. One of these patients was examined three times during the course of her illness. At the height of the disease and impairment of hepatic function, a disturbance of uric acid partition prevailed, while uric acid partition was normal at the onset and during recovery. The present material is too scant to permit definite conclusions as to the relation between hepatic function and uric acid partition.

The next subgroup is represented by 4 persons with malignant growths (patients 202, 203, 204 and 205) characterized by icterus of long duration, enlargement of the liver and considerable loss of weight. In 3 patients the diagnosis was confirmed by operation. In 2 patients of this group, the total uric acid is low. The uric acid partition is normal only in patient 202 and abnormal in the others, in whom the bound uric acid ranges between 31 and 40 per cent of the total uric acid. The highest figure, 40 per cent, is found in patient 205, in whom the total uric acid is only 2 mg. per hundred cubic centimeters. That low values for total uric acid are not necessarily accompanied by relatively high

TABLE 6.—Uric Acid Partition in Patients with Hepatic Disease

Pa- tient No.	Sex; Age, Yr.	Condition	Date	Uric Acid Partition			Bound Uric Acid, Percent-	Laboratory Data					Clinical Data
				Total Uric Acid, Mg./ 100 Cc.	Fil- trable, Mg./ 100 Cc.	Nonfil- trable, Total Mg./ 100 Cc.		Icteric Index	Cholesterol, Mg./100 Cc.		Galac- tose Toler- ance, Gm.		
									Total	Ester			
201	♀ 12	Cholelithiasis; toxic hepatitis; diabetes mellitus	11/17/40	4.2	3.7	0.5	12	94	195	45	7.1	Diabetes 4 mo. and icterus and chills 3 days before admission; liver palpable 3 fingerbreadths below costal margin; 2 biliary calculi in cholecystogram; positive reaction for tyrosine in urine; gradual improvement	
202	♂ 59	Carcinoma of head of pancreas; diabetes mellitus	11/11/40	5.6	4.8	0.8	14	24	250	130	...	Diabetes 2 yr. and progressive painless jaundice a few days before admission; exploration: hard mass in head of pancreas, no gallstones	
203	♀ 63	Carcinoma of gallbladder; dia- betes; hypertension	1/8/41	3.7	2.5	1.2	32	17	...	..	...	Jaundice 4 wk. before admission; liver palpable 3-4 fingerbreadths below costal margin; laparotomy; carcinoma of gallbladder; blood sugar, 310 mg./100 cc.; blood total protein, 7.1 Gm./100 cc.	
204	♂ 70	Carcinoma of head of pancreas; diabetes	1/27/41	2.9	2.0	0.9	31	21	170	90	...	Loss of weight; icterus; liver palpable 4 fingerbreadths below costal margin; phosphatase, 58 King-Armstrong units	
205	♂ 53	Carcinoma of head of pancreas; tertiary syphilis	1/24/41	2.0	1.2	0.8	40	45	460	..	3.5	Syphilis for many years; pain, loss of weight and anorexia 3 mo. before admission; operation: large firm mass in head of pancreas and greatly extended gallbladder, containing 500 cc. of white bile	
206	♀ 55	Pyelophlebitis; suppurative cholan- gitis; cholelithiasis	9/19/40	2.6	1.4	1.2	46	45	170	50	...	Recurrent pain in right upper quadrant of abdomen for 20 yr.; episode of pain, with chills, fever, vomiting and icterus 2-3 wk. before admission; autopsy: pyelophlebitis, thrombotic occlusion of portal vein, perforation of gallbladder and pericholecystic abscess; temperature 103-106 F.	
207	♀ 52	Cholangitis; cholangiolitis	12/29/40 1/10/41	3.8 4.6	3.0 4.0	0.8 0.6	21 13	..	...	..	...	Cholecystectomy 5 yr. ago; painless increasing jaundice and dark urine 3 wk. before admission; loss of weight; temperature, 101 F.; small shrunken gallbladder; common duct dilated to about 3/4 in. in diameter; no evidence of stones; biopsy of liver: acute and chronic cholangiolitis and pericholangiolitis; no evidence of cirrhosis; biopsy of common duct: chronic and acute inflammation of wall	
208	♂ 48	Cirrhosis of liver; syphilis; psoriasis; pyelonephritis	9/12/40	7.3	0.7	0.6	8	8	125	65	4.7	Syphilis for 20 yr.; ascites, edema, hematemesis and melena 3 days prior to admission; liver and spleen enlarged; Takata-Ara reaction positive (+++); test for bilirubin in urine negative	
209	♂ 65	Cirrhosis of liver; macrocytic anemia	9/12/40	6.7	5.8	0.9	13	9	230	145	2.9	History of gallbladder disease for 20 yr.; painful jaundice 10 yr. ago; liver palpable 4 fingerbreadths below costal margin; spleen enlarged	
210	♂ 33	Cirrhosis of liver	9/22/40	2.9	2.2	0.7	24	15	170	60	...	Second admission because of reaccumulated ascites and severe edema of lower extremities; cachexia; liver and spleen palpable; total protein in blood, 5.6 Gm./100 cc.; positive reaction for bilirubin in urine	
211	♂ 38	Cirrhosis of liver; toxic hepatitis	11/12/40 12/11/40	4.1 1.6	3.4 3.6	0.7 1.0	17 22	20	190	70	...	Addicted to alcohol since age of 7; edema for 4 wk. and jaundice and acholic stools 3 wk. before admission; loss of 35 lb. in 8 mo.; liver enlarged to umbilicus; spleen palpable 2 fingerbreadths below costal margin; necropsy: Laennec's cirrhosis; Wassermann reaction positive (++++)	
212	♂ 43	Cirrhosis of liver; syphilis	11/21/40	5.6	1.1	1.2	21	..	...	..	9.7	Gonorrhea and syphilis 18 yr. before admission, with many specific treatments since; jaundice of 5 mo. duration during antisyphilitic therapy 1 yr. before admission; tarry stools 1 day before admission; liver palpable 1 1/2 fingerbreadths below costal margin; no icterus; Wassermann reaction positive (++)	

213	♀ 26	Cirrhosis of liver	12/17/40 12/25/40	3.3 2.8	2.1 2.6	0.9 0.2	27 7	28 ..	675 500	80 65	1.2	Admitted to alcohol for 3 yr.; ascites and edema; alcoholic polynephritis; liver enlarged; gradual improvement
214	♀ 43	Cirrhosis of liver	1/15/41 1/21/41	3.8 3.8	3.1 2.8	0.7 1.0	18 26	9	335	155	...	Attacks of hunger, weakness, sweating, palpitation and anxiety; nodular liver, palpable down to umbilicus; hard sharp spleen
215	♀ 45	Cirrhosis of liver; subacute bacterial endocarditis	1/16/41 1/28/41 2/ 7/41	1.3 3.6 3.6	3.6 2.7 2.7	0.7 0.9 1.2	16 25 31	25	225	75	...	Ascites, edema; progressive impairment of general condition; positive reaction for tyrosine in urine; blood content (mg./100 cc.) of total protein 5.6, albumin 2.5, globulin 3.1; death from cholelith; autopsy: Laennec's cirrhosis of liver, splenomegaly, dilatation of esophageal veins and subacute bacterial endocarditis of aortic valve superimposed on chronic rheumatic valvulitis
216	♀ 33	Cirrhosis of liver	1/19/41 1/33/41	7.5 6.7	6.2 5.0	1.3 1.7	17 25	14	405	100	5.3	Liver palpable 2-3 fingerbreadths above umbilicus; spleen palpable; no definite ascites; icterus slowly subsiding; general condition improved
217	♀ 41	Cirrhosis of liver; diaphragmatic hernia	1/ 3/41 2/ 5/41	3.6 3.1	2.0 2.8	1.6 0.6	44 18	8	300	175	5.6	Liver enlarged, spleen palpable; exploratory laparotomy: cirrhotic liver, hob-nailed in appearance; biopsy of liver: obliteration of lobular architecture with infiltration of periportal fields with plasma cells, lymphocytes and leukocytes, suggestive of early cirrhosis
218	♀ 60	Biliary cirrhosis of liver; obstructive jaundice of long duration	1/ 1/41 1/ 8/41 1/20/41	3.5 3.7 3.9	2.4 2.3 2.9	1.1 1.4 1.0	31 38 26	28 9	260	..	1.7	Cholecystectomy 2 yr. before admission; postoperative spontaneous biliary fistula; fever, chills, light stools and dark urine for several weeks; liver enlarged; biopsy: acute and chronic pericholangitis with fibrosis of the periportal fields; slow improvement
219	♂ 57	Metastatic carcinoma of liver; cirrhosis of liver	1/27/41	3.1	2.1	1.0	32	18	345	115	1.0	Heavy drinker until 9 yr. before admission; loss of weight, anorexia, icterus; mass in epigastrium; diagnosis proved by biopsy
220	♀ 54	Lymphatic leukemia; obstructive jaundice	12/12/40 12/25/40	8.8 4.8	6.3 3.8	2.5 1.0	28 21	40 13	335	..	2.45	Lymphatic leukemia of 1 yr. duration; nausea, dark urine and icterus 2 wk. prior to admission; liver 2½ fingerbreadths below costal margin, spleen enlarged to umbilicus; after roentgen therapy liver decreased in size, icterus subsided
221	♂ 19	Toxic hepatitis due to gold	12/ 5/40	5.2	3.7	1.5	29	34	190	70	4.6	Arthritis for 6 yr.; series of gold injections 8 wk. before admission; chills, temperature of 102 F. and progressive icterus 4 days before admission; liver palpable; icterus slowly subsiding
222	♂ 23	Hepatitis, subsiding	9/12/40	5.8	4.8	1.0	17	30	210	60	6.1	Yellow skin, light stool and dark urine 2 wk. before admission; liver hard, enlarged to point 1 fingerbreadth below costal margin; gradual improvement
223	♂ 37	Toxic hepatitis, subsiding	9/12/40	6.2	5.3	0.9	15	16	230	55	5.8	Anorexia, nausea and dark urine 11 days before admission; jaundice 3 days later; liver hard, enlarged; gradual improvement; positive reaction for bilirubin in urine
224	♀ 34	Toxic hepatitis due to cinchophen	11/ 8/40	3.6	3.2	0.4	11	9	135	25	4.3	Took acetylsalicylic acid and cinchophen for relief of sciatica; anorexia, icterus, pruritus; total dose of cinchophen, 64 grains in 5 days; examined in subsiding state; positive reaction for tyrosine in urine
225	♂ 31	Toxic hepatitis	1/12/40 1/17/40	5.8 5.8	4.9 4.0	0.9 1.8	16 31	26 12	280	155	Normal	Dysentery 6 mo. prior to admission; jaundice 3 mo. later; icterus subsiding
226	♀ 69	Hepatitis	1/20/41 1/28/41 2/ 5/41	6.1 4.1 4.3	5.1 2.4 4.0	1.0 1.7 0.3	16 41 7	85 70 35	190 170 200	..	1.5 8.3	Recurrent painless jaundice; icterus slowly subsiding; course complicated by infection caused by Bacillus coli; urinalysis: (1/20) positive reaction for bilirubin (++++), and urobilin (1:4), (1/28) positive reaction for bilirubin (++++), (2/5) positive reaction for bilirubin
227	♀ 33	Hepatitis	1/22/41 1/30/41 2/ 7/41	2.6 3.4 3.2	2.2 2.7 2.7	0.4 0.7 0.5	15 21 16	70 45 21	170	30	2.1	Long-lasting, mild hepatitis, with complete remission of symptoms; urinalysis: (1/22) positive reaction for bilirubin (++++), and urobilin (1:4), (2/7) positive reaction for bilirubin and urobilin (1:10)
228	♂ 55	Hepatitis	12/27/40	5.1	4.1	1.0	20	44	...	..	...	Jaundice subsiding; no pain, no masses, liver not palpable; urinalysis: positive reaction for bilirubin and urobilin (1:80)



percentages of bound uric acid is evidenced by the values for persons without hepatic disease (subjects 3 and 19 in table 4 and patients 102, 112 and 114 in table 5). The long-lasting icterus and the associated hepatic damage must be responsible for the abnormalities of uric acid partition in the patients with carcinoma with biliary obstruction.

Among the other patients with hepatic disease, abnormal uric acid partition was observed but twice, once in a patient with suppurative cholangitis and pylephlebitis with severe icterus and a low titer of cholesterol ester. This patient, who died, had a total uric acid content of 2.6 mg. per hundred cubic centimeters and a bound uric acid value of 46 per cent (patient 206). The other patient had lymphatic leukemia (patient 220) with icterus, which subsided slowly on roentgen treatment of the liver. At the height of the disease, the total uric acid was elevated to 8.8 mg. per hundred cubic centimeters, and the bound uric acid was 28 per cent of the total. During recovery, when the icteric index decreased rapidly from 40 to 13 units, the total uric acid dropped to 4.8 mg. per hundred cubic centimeters and the bound uric acid to 21 per cent of the total.

#### URIC ACID PARTITION IN PATIENTS WITH GOUT

The significance of uric acid metabolism in the etiology of gout is a subject of controversy, but it is generally acknowledged that gout is associated with abnormalities of uric acid metabolism. In the course of almost two years we were able to observe 10 patients with typical gout. A few persons with atypical gout were purposely disregarded. The 10 patients selected had a history of periodic attacks of pain, particularly in the big toes, with reddening and swelling. They responded promptly to a purine free, low fat diet<sup>29</sup> plus administration of colchicine. The total uric acid in these patients (table 7) is markedly elevated and varies from 5.1 to 16.4 mg. per hundred cubic centimeters, the average for all patients being 9.2 mg. per hundred cubic centimeters, almost double the average value for total uric acid in the serum of normal persons. The high level of the total uric acid is associated with an elevation of the free uric acid to 14.4 mg. per hundred cubic centimeters, with an average of 7.4 mg. The bound uric acid ranges between 0.1 and 3.6 mg. per hundred cubic centimeters, with an average of 1.8 mg., which is double the average bound uric acid in normal persons. Yet in relation to the total uric acid, the bound uric acid averages 20 per cent, compared to a ratio of 16 per cent in normal serum. The patients in table 7 present a greater variety of values both for the total uric acid and for the uric acid partition than does any other group of our subjects.

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29. Adlersberg, D., and Ellenberg, M.: Effect of Carbohydrate and Fat in the Diet on Uric Acid Excretion, *J. Biol. Chem.* **128**:379-385, 1939.

The observation of patients with gout over a prolonged period and the correlation of the findings with the clinical course are of interest. Patient 301 has been observed for half a year. His total uric acid is

TABLE 7.—*Uric Acid Partition in Patients with Gout*

Patient No.	Sex; Age, Yr.	Date	Uric Acid Partition				Clinical Data
			Total Uric Acid, Mg./100 Cc.	Filterable, Mg./100 Cc.	Non-filterable, Mg./100 Cc.	Bound Uric Acid, Per cent of Total Uric Acid	
301	♂ 60	9/23/40	10.0	8.7	1.3	13	Lithopexy for vesical calculi February 1940; attacks of pain and swelling of right big toe, ankle and elbow for past few years; tophi on ears; prompt response to colchicine
		11/28/40	10.7	9.4	1.3	12	
		1/ 2/41	10.8	8.2	2.6	24	
		1/ 4/41	10.4	9.0	1.4	14	
		1/18/41	11.6	10.2	1.4	12	
		2/ 6/41	10.0	8.3	1.7	17	
302	♂ 65	3/29/41	11.6	10.0	1.6	14	Polycythemia for 7 yr.; hemoglobin concentration, 110 per cent; red cell count, 7,750,000; numerous tophi over most of joints; multiple cysts of kidneys with deposition of uric acid revealed at necropsy
		9/26/40	13.0	10.7	2.3	18	
303	♂ 67	12/18/40	7.8	6.5	1.3	16	History of arthritis of big toe; good response to colchicine
304	♂ 51	12/23/40	5.8	4.0	1.8	31	Pain in feet for 4 yr., with redness and swelling; later swelling and redness of a few finger joints; prompt improvement on anti-gout regimen and colchicine therapy
		2/ 7/41	5.5	1.9	3.6	65	
		3/ 1/41	5.7	4.2	1.5	26	
305	♂ 50	12/29/40	16.4	14.4	2.0	12	Redness of skin of several days' duration, with cellulitis; knee swollen, red and painful and fever present during observation
306	♀ 50	1/ 6/41	5.6	4.2	1.4	25	Attacks of pain in right knee and both shoulders and fingers of both hands, particularly the right ones; improvement on low purine, low fat diet and colchicine therapy
		2/ 5/41	6.3	5.3	1.0	16	
307	♀ 61	1/12/41	6.0	4.4	1.6	27	Pain in right knee and foot; obesity; sudden pain in right toe, hypertension and arteriosclerosis; improvement on gout diet
		1/24/41	5.1	3.4	1.7	33	
308	♂ 48	1/13/41	9.0	6.1	2.6	29	Pains starting in left big toe, ankle and knee and swelling and redness for 10 yr.; tophi in ears; definite improvement on gout diet and colchicine therapy
309	♂ 54	1/ 6/41	9.5	7.1	2.4	25	Obesity; pain in left big toe and foot; improvement on therapy with mild mercurous chloride and sodium bicarbonate; erosion of head of fifth left metatarsal for about 5 mm. (tophus)
		1/24/41	9.6	7.5	2.1	22	
310	♂ 34	4/ 1/41	10.3	10.2	0.1	1	Attacks of swelling, tenderness and reddening of left ankle; obesity; improvement on gout regimen
		4/ 3/41	10.4	9.1	1.3	13	
		4/17/41	9.4	6.9	2.5	27	
		4/25/41	9.7	8.1	1.6	17	

considerably elevated, to 10.0 to 11.6 mg. per hundred cubic centimeters. The uric acid partition is fairly constant, the bound uric acid being 1.3 to 1.7 mg. per hundred cubic centimeters, or 12 to 17 per cent of the total uric acid. Only on one occasion, during an attack of gout, was there an elevation of the bound uric acid to 2.6 mg. per hundred cubic

centimeters, or 24 per cent of the total uric acid. On initiation of colchicine therapy the symptoms promptly subsided, and two days later and thereafter the uric acid partition was normal. The elevation of the level simultaneously with the attack is of interest, although the value of 24 per cent bound uric acid falls just within the upper limit of normal.

Patient 304 was examined three times. During the whole period he was never completely free of symptoms. Although the total uric acid content was normal, the uric acid partition was abnormal, particularly on the second examination. On this occasion the patient had only 1.9 mg. of free uric acid, as against 3.6 mg. of bound uric acid, per hundred cubic centimeters. The bound uric acid represented 65 per cent of the total uric acid, the only instance of a reversal of the ratio. The lowest figure for bound uric acid in this patient was 26 per cent. It is noteworthy that in this patient with typical gout a normal total uric acid content was associated throughout the period of observation with an abnormal uric acid partition. Patient 307 presents a similar picture, normal values for the total uric acid content but an abnormal bound uric acid ratio of 27 to 33 per cent. On the other hand, one should remember that hyperuricemia, even of an extremely high degree (13.0 and 16.4 mg. per hundred cubic centimeters) may be associated with a normal uric acid partition (18 and 12 per cent, respectively), as in patients 302 and 305.

In the normal group individual constancy of uric acid partition was noticed. On the contrary, in a patient with gout, the total uric acid content may remain quite constant, while the uric acid partition shows considerable fluctuation. This is exemplified by patients 301 and 304 and, in particular, patient 310. The last-named patient was admitted with severe pain in one foot and was given colchicine immediately. The first specimen of blood was drawn after four days of treatment and yielded a total uric acid content of 10.3 mg. per hundred cubic centimeters, with almost complete absence of bound uric acid; in other words, the entire uric acid content was ultrafiltrable, a unique finding. Three days later the bound uric acid had returned to the normal value of 13 per cent. Because of recurrence of pain a few days later, the patient was given cinchophen. The total uric acid content diminished moderately, and the bound uric acid increased to 27 per cent. After a second course of colchicine, the bound uric acid dropped to 17 per cent, with no change in the total uric acid content. We surmise that the beneficial effect of colchicine on uric acid diathesis is due to lowering of the bound, rather than of the total, uric acid titer.

A review of data on the patients with gout reveals (*a*) occurrence of the highest absolute figures for total, as well as for free and for bound, uric acid, (*b*) absence of parallelism between the degree of hyper-

uricemia and the disturbance of uric acid partition and (c) great variability in the amount of bound uric acid, probably connected with the clinical course of the disease and with therapeutic measures. We wish to emphasize that patients with typical gout, such as patients 304, 306 and 307, have normal figures for total uric acid but abnormally high values for bound uric acid. Under these circumstances the ratio may form a valuable criterion for the diagnosis of gout. This problem is the subject of further studies.

#### COMMENT

Consideration of the entire material presented in this paper permits the following statements: Comparatively constant uric acid partition is a characteristic of the normal blood serum. Among the pathologic conditions considered, particularly gout and hepatic damage bring about disturbance of the uric acid partition, characterized by a diminution of the free, and elevation of the bound, uric acid fraction. The liver is known to play an important role in purine metabolism; hence, hepatic disease may result in disturbances of this metabolic domain. Gout, in turn, may be accompanied by signs of hepatic damage. Whatever the primary disturbance of uric acid metabolism may consist of in hepatic disease, it manifests itself in a change of uric acid partition. Whether the analogous variations in persons with gout are caused by a dysfunction of the liver cannot yet be decided.

The real nature of the bound uric acid in the blood is as yet unknown. For the same reason, no further explanation can be offered for the elevation of this fraction in the patients with the pathologic conditions mentioned. Nevertheless, it is interesting to speculate on possible common etiologic factors in hepatic disease and gout. Further investigations will be required to establish the place and the importance of uric acid partition in clinical diagnosis along the suggested lines.

#### SUMMARY

In 22 normal subjects the nonultrafiltrable (bound) uric acid varied between 4 and 24 per cent of the total uric acid content of the serum, the average being 16 per cent. There is a certain individual constancy of uric acid partition.

In 25 patients with miscellaneous pathologic conditions the uric acid partition was normal. Abnormally high values for the nonultrafiltrable fraction occurred only in 1 patient with atypical exophthalmic goiter and in 1 with multiple myeloma.

Abnormal uric acid partition was observed in about half of the patients with hepatitis, cirrhosis of the liver and prolonged obstructive jaundice, also in a patient with suppurative cholangitis and in 1 with

leukemia with icterus. A high titer of bound uric acid is not a persistent finding in the individual patient with hepatic damage. Clinical improvement may be associated with a decrease of bound uric acid and vice versa.

In 10 patients with gout, elevation of total, and correspondingly of bound, uric acid prevailed. The bound uric acid varied from 1 to 65 per cent of the total uric acid content. Gout with extreme hyperuricemia may be associated with a normal uric acid partition; on the other hand, patients with gout in whom the total uric acid content is not elevated may be distinguished by a high bound uric acid ratio. The diagnostic significance of such findings is suggested. A possible relation between the clinical course, the therapeutic measures and the bound uric acid fraction is discussed.

Dr. Max Ellenberg and Miss Lena Sharney assisted in obtaining and analyzing some of the specimens.

# MULTIPLE POLYPS OF THE ESOPHAGUS

## REPORT OF A CASE WITH COMPLICATING RECURRENT GASTROINTESTINAL HEMORRHAGES

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Gastrointestinal hemorrhage from esophageal polyps is exceedingly rare. We wish to present the case of a girl who suffered repeated gastrointestinal hemorrhages over a period of five years. The bleeding was originally attributed to esophageal varices, but subsequent clinical study revealed multiple polyps of the esophagus as the cause of hemorrhage. These polyps were successfully removed by fulguration, which rendered the esophagus practically normal, and the patient has been free from hemorrhage since this procedure.

### REPORT OF CASE

The patient, a girl of 10, was first admitted to the pediatric ward in the service of Dr. Charles Weymuller on July 27, 1935 and discharged on November 3. Her illness dated back to 1928, at which time jaundice, abdominal distention and engorgement of the veins of the abdominal wall were said to have been present. Blood was noted in the stool at that time. The first episode lasted several months, after which the patient felt entirely well until May 10, 1935. At this time pallor and jaundice were noted, and blood was once again present in the stool. The episode was transient, and the patient was well until the day of admission, when she complained of dizziness and vomited about half a glass of bright red blood. This was preceded by vague epigastric pain, which disappeared after the hematemeses.

The only other illnesses in the patient's past history were measles and otitis media.

On examination the patient appeared well nourished but weak and pale. There were two decayed teeth. The lungs were normal. The heart was not enlarged; the sounds were of fair quality, and no murmurs were heard. The abdomen was soft and not distended. There was no tenderness. The spleen was enlarged, firm and smooth and was not tender. It was felt 5 fingerbreadths below the costal margin. The liver could not be palpated. The extremities were normal.

The red cell count was 3,200,000 and the hemoglobin concentration 58 per cent. The white cell count was 13,600. A differential count showed 87 per cent polymorphonuclear neutrophils and 12 per cent lymphocytes. There were no abnormal

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cells. The platelet count was 262,500. The percentage of reticulocytes was 1. The urine was normal. The stool was grossly bloody, and clots were present. The stool remained bloody as late as July 31, and by this date the hemoglobin concentration had fallen to 25 per cent and the red cell count to 1,500,000. The white cell count was 62,000, and the differential count was normal. The level of urea nitrogen in the blood was 24.9 mg. per hundred cubic centimeters, and the levels of calcium, phosphorus and sugar were not significantly altered. The icterus index was 4. Blood continued to be present in the stool and on July 31 a direct transfusion of 150 cc of blood was given. No improvement was noted,

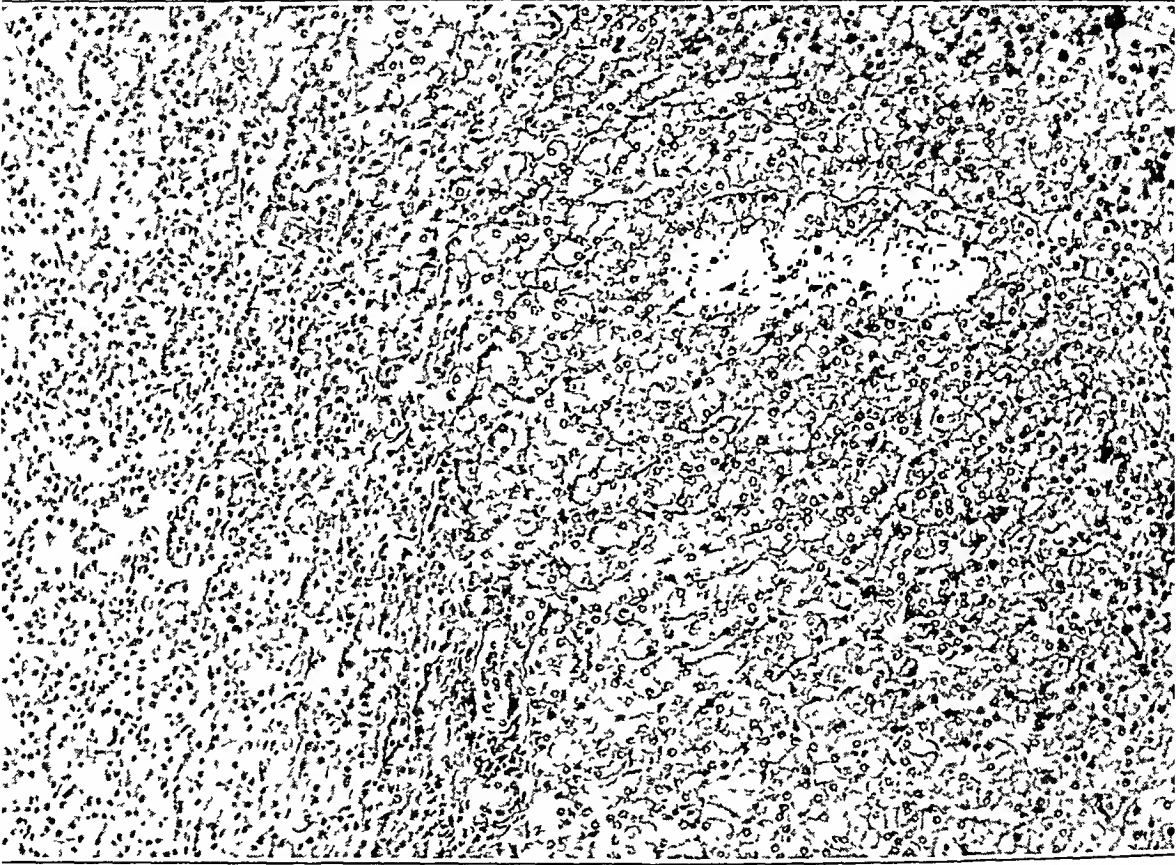


Fig. 1.—A section of a biopsy specimen taken from the liver.

and by August 2, air hunger was present and the patient was restless and prostrated. A soft blowing systolic murmur was heard at the apex. The spleen was still palpable. Dulness was noted in both flanks, and a fluid wave was present. Another transfusion of 150 cc was given. By August 7, a week later, gross blood was no longer visible in the stool, but occult blood was still present. The physical findings associated with the presence of abdominal fluid were still in evidence.

The patient was placed on liver and iron therapy. By August 19 her condition had improved considerably. The spleen was still palpable, but the signs of ascites were less marked. The hemoglobin concentration was 51 per cent and the red cell count 2,600,000. The stool still contained occult blood. Steady improvement continued, and by September 9 the hemoglobin concentration had risen to 75

per cent and the red cell count to 3,620,000. The white cell count was 3,600 and had ranged between 3,000 and 4,500 for about two weeks. Occult blood was still present in the stool.

The diagnosis at this time was considered to be Banti's syndrome and hemorrhage from esophageal varices. The patient's condition was then good enough to warrant operation, and this was done on September 19. A left upper rectus incision was made, and the spleen, which was fixed by numerous fibrous adhesions to the surrounding tissues, was removed. It was stated in the report of the operation that the adhesions were old but moderately vascular. Two small

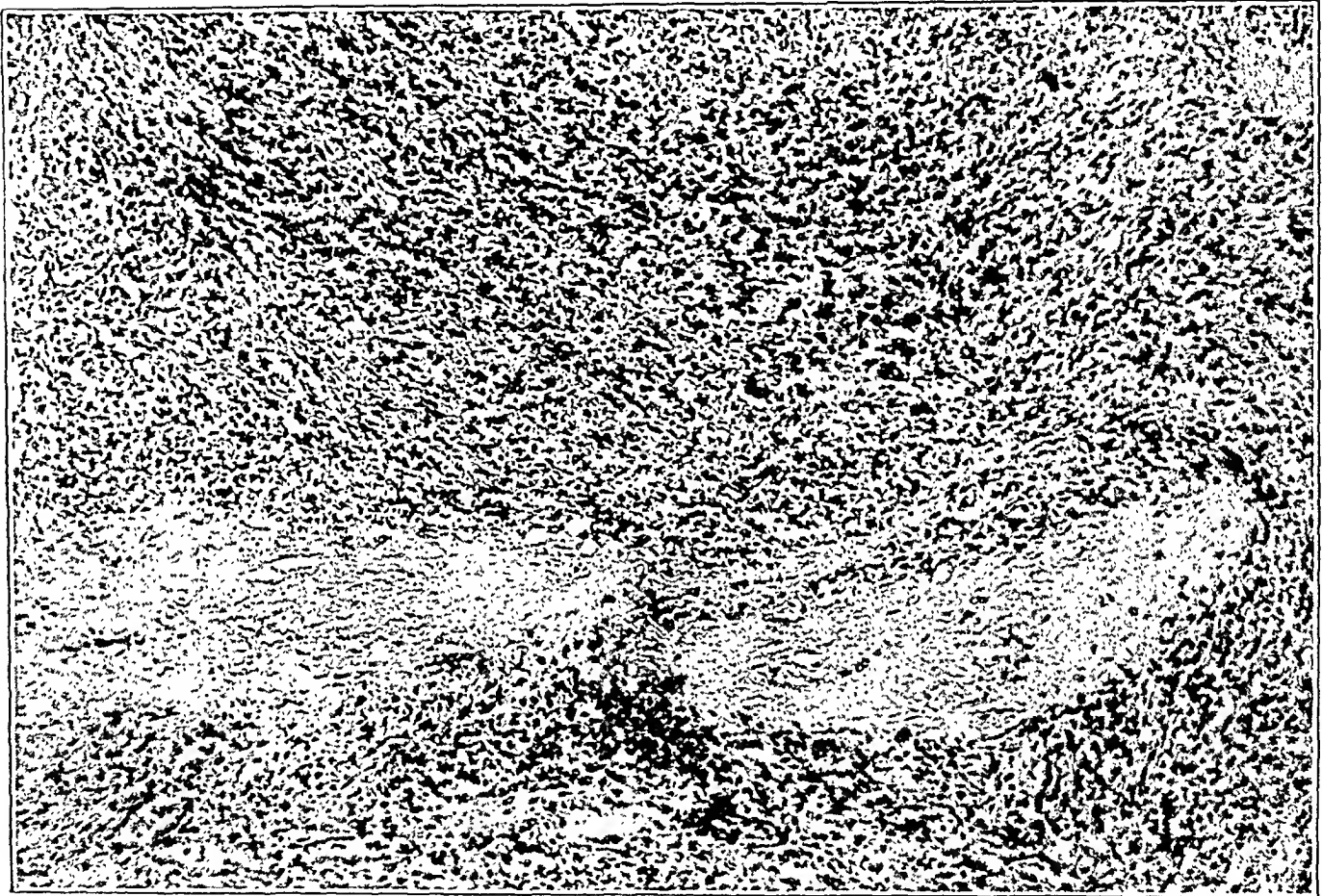


Fig. 2.—A section of the spleen.

accessory spleens measuring about 1 cm. in diameter were also removed. No abdominal fluid was found. The liver appeared grossly normal. A biopsy specimen was taken, however. Microscopic study of this specimen (fig. 1) showed distortion of structure, cellular infiltration around the smaller ducts and degeneration of many liver cells. The spleen (fig. 2) showed a general thickening of the fine reticulum and also of the larger trabeculae. There was a mild to moderate degree of periarterial fibrosis, and the sinuses were distinctly enlarged.

The patient's postoperative course was uneventful. The stool was first reported as giving a negative reaction for occult blood on September 28, nine days after operation. On October 1 the patient passed about 8 cc. of dark brown urine, which on microscopic examination was seen to be filled with red and with white



blood cells. At this time the patient noticed lumbar pain on the right side which became severe and radiated to the right loin. There was marked tenderness to pressure over the entire region of the right kidney. By October 5, the pain had disappeared and no more red cells were seen in the urine, though white cells were present for a few days more. By October 11, the patient was asymptomatic and the urine was clear. From this time on no untoward incidents occurred, and on discharge on November 3, 1935, the red cell count was 4,970,000, the hemoglobin concentration 78 per cent and the white cell count 11,000. The differential count was still normal, as it had been throughout the patient's hospitalization, though a shift to the left had been noted at times. No abnormal cells were seen at any time. The clotting time, the results of the fragility test and the bleeding time were all within normal range. The diagnoses at the time of discharge were (1) Banti's syndrome, (2) splenectomy and (3) right renal infarct.

The patient was admitted for the second time on May 19, 1937 and discharged on June 10. She was well until the night before entry, when vague epigastric distress developed and she felt nauseated. An enema given at this time yielded some tarry feces. Two hours after the enema, the patient had a bowel movement, and the stool was described as tarry. She rapidly became weak and was brought to the hospital the following morning. On examination the patient appeared anemic. A systolic murmur was heard at the apex and at the pulmonary area. The abdomen was not distended or tender. There was no ascites or venous engorgement. The liver and the kidneys could not be felt. Rectal examination showed nothing of note, though some tarry fecal material was seen on the glove.

The red cell count was 3,340,000 and the hemoglobin concentration was 52 per cent. The white cell count was 16,400. The differential count was normal. A tourniquet test showed no evidence of increased capillary fragility. The clot retraction time was four hours. The stool remained tarry until May 21, and on this date, the hemoglobin concentration was as low as 44 per cent and the red cell count 2,950,000. A brown stool was first noted on May 23. The patient improved progressively, and on June 4, the hemoglobin concentration was 61 per cent and the red cell count was 4,500,000. An esophagram was made on June 8; a fairly large constant defect measuring 2 by 1 cm. was noted in the distal portion of the esophagus. There were some irregularities in the anterior and the posterior portion of the lower part of the esophagus suggesting smaller varices (fig. 3). The patient was discharged on June 10, with the diagnoses of Banti's syndrome and hemorrhage from an esophageal varix.

The child was symptom free until the night of Jan. 29, 1938, when severe cramplike pain suddenly developed in the left lower quadrant of the abdomen. On the morning of January 30 she suddenly became nauseated and vomited about two glasses of bright red blood containing many clots. She was immediately brought to the hospital. The patient appeared listless and pale. The physical examination failed to reveal anything different from the results of previous physical examinations. Marked secondary anemia was again present; the red cell count was 1,580,000, and the hemoglobin concentration, 26 per cent. The white cell count was 26,000, and the differential count showed a shift to the left, with 84 per cent neutrophils. The blood urea nitrogen was 20.2 mg. per hundred cubic centimeters. The patient gradually improved on supportive therapy, and blood disappeared from the stool. A transfusion of 400 cc. of blood was given on February 1. A picture of the abdominal wall taken at this same time under infra-red rays showed no evidence of increased venous circulation. A roentgenogram of the chest

showed nothing abnormal, and barium sulfate studies of the esophagus once again revealed irregularities which were interpreted as varices.

Due to the patient's repeated episodes of hematemesis it was decided to operate once again in an attempt to prevent further esophageal hemorrhages by ligation of the coronary vein. On March 9 an exploration was performed by Dr. E. Goetsch through a right upper rectus incision. The peritoneum was opened without difficulty, and then numerous adhesions were encountered in the peritoneal cavity. The adhesions were so abundant that the abdominal viscera to the left of the midline could not be visualized. An attempt was made to visualize the stomach, but after only one third of the lesser curvature was exposed the procedure was abandoned because of the numerous vascular adhesions. The liver was noted to be slightly enlarged



Fig. 3.—A roentgenogram of the barium-filled esophagus, demonstrating translucent areas in the lower portion.

and somewhat soft. A biopsy specimen was taken and on microscopic examination showed mild degeneration. It was decided to do an omentopexy. The omentum was freed. A small incision was made in the peritoneum and the posterior rectus sheath, and the omentum was then brought through this incision and placed beneath the rectus muscle. It was felt that the absence of free fluid, the rather normal appearance of the liver and the absence of dilated veins were not consistent with the diagnosis of Banti's syndrome. The patient's postoperative course was uneventful, and she was discharged on March 23, 1938. The final opinion was undiagnosed disease and hemorrhage from an unknown cause.

The patient's next admission was on Aug. 28, 1939, on which day severe cramplike pain developed in the right lower quadrant of the abdomen associated

with nausea. There was no vomiting. The abdomen was somewhat distended. The percussion note was tympanitic, and borborygmus was present. There was no spasm, but tenderness was present just below and to the right of the umbilicus on moderate pressure. The red cell count was 5,100,000 and the hemoglobin concentration 99 per cent. The white cell count was 23,600. There was a shift to the left, with 86 per cent neutrophils. No abnormal cells were seen. A flat plate of the abdomen revealed nothing abnormal. It was thought that the patient might have either intestinal obstruction or acute appendicitis. The pain, however, subsided rapidly, and operation was withheld. Suddenly on September 3 the patient cried out and became unconscious. Her skin was pale and cold and clammy. The pulse was barely perceptible, and the rate was 130 per minute. The blood pressure was 70 systolic and 30 diastolic. Consciousness returned in a few minutes, and the patient was unable to say why she cried out. Examination revealed nothing of note. However, about one-half hour after returning to consciousness, the patient vomited nearly 5 fluidounces (150 cc.) of bright red blood. She was given supportive therapy, and one transfusion of 300 cc. of blood. She improved gradually, and the stool gave a negative reaction to the benzdene test on September 16. She was discharged on September 17.

The patient had to be readmitted on Jan. 27, 1940 for pain in the right lower quadrant of the abdomen similar to that occurring on her preceding admission. Examination of the abdomen revealed only moderate tenderness in the right lower quadrant. While in the hospital she had several similar bouts of pain, all of which subsided rapidly. She was discharged on February 4, with a final diagnosis of abdominal pain of unknown cause.

The patient's sixth admission to the hospital was on February 28. Two days prior to this, she had again had cramplike abdominal pain, and on the night of admission she vomited about 1 pint (470 cc.) of bright red blood. Shortly after admission she again vomited about 1 pint of blood. She was in shock. The blood pressure was 70 systolic and 50 diastolic, and the pulse rate was 116 per minute. The abdomen was soft and not distended. There were no masses or tenderness. The liver and the kidneys could not be palpated. The hemoglobin concentration was 49 per cent, and the red cell count was 3,400,000. The stool was tarry and gave a positive reaction for blood. Hepatic function tests yielded normal results, including the hippuric acid test, the galactose tolerance test and a dye excretion test. The patient's improvement was gradual, and no untoward incidents occurred. Barium sulfate studies of the esophagus once again revealed the irregularities previously described. Gastrointestinal roentgenograms and a barium sulfate enema showed nothing abnormal. It was decided to perform an esophagoscopy examination, and if varices were present it was planned to have them sclerosed by the method described by Moersch.<sup>1</sup> Esophagoscopy was performed for the first time on May 20, by Dr. R. L. Moorhead, and numerous pale, glistening projections of irregular size and shape were seen studding the surface of the mucosa. These were most numerous in the lower third of the esophagus. Some of these projections were sufficiently large to occlude the lumen. It was the opinion of the operator that these masses were polyps. Esophagoscopy was again done on June 6, and a biopsy specimen was taken. No sooner had the specimen been taken than there was a huge gush

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1. Moersch, H. J.: Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. 15:177 (March 20) 1940.

of dark venous blood, and within a few minutes the patient lost approximately 1,500 cc. of blood. The patient's pulse rose with great rapidity and soon became imperceptible, while the blood pressure dropped until it was unobtainable. Respirations became irregular, and the patient's condition was grave. Emergency measures were instituted. Epinephrine was given. The esophagus was packed with gauze from the cardia to the mouth. An infusion of physiologic solution of sodium chloride was begun while blood was obtained, and 500 cc. of blood was given before the patient left the operating room. The patient was heavily narcotized and treated with two further transfusions of 500 cc. each. Nothing was given by



Fig. 4.—A section of the biopsy specimen taken from an esophageal polyp. Note the blood spaces in the squamous epithelium.

mouth. Her condition improved rapidly, and by June 8, she was able to take fluids. On June 10, esophagoscopy was again performed. No evidence of bleeding was noted, and the sponges which had been used to pack the length of the esophagus could not be seen. The report of the histologic picture of the biopsy specimen, by Dr. J. N. Pierce, was as follows (fig. 4): "Gross description: The specimen consists of a small fragment of friable, wrinkled, membranous tissue less than 1 cm. in size. Microscopic description: In one small area approximately two low power fields in size the squamous epithelium lining the esophagus is thickened to three to four times its normal width. In the epithelium there are thin-walled endothelium-lined spaces distended with blood and accom-

panied by a delicate fibrous stroma. There is no penetration of the underlying tissue by the epithelium, and the basement membrane is intact." Dr. Pierce stated that he could not make a diagnosis of polyp from the specimen itself and that we would have to depend on the gross appearance at esophagoscopy. The esophagoscopists were reluctant to secure any more tissue for biopsy after the first severe hemorrhage. The decision was made, though not without trepidation, to fulgurate as many of the polyps as possible. Thereafter, the patient was



Fig. 5.—The esophagus after fulguration of the polyps, appearing almost normal.

operated on sixteen times by Dr. Moorhead and his staff, and the growths were gradually fulgurated from the upper portion of the esophagus to the cardiac end of the stomach. At the time of discharge on November 22, there was little or no evidence of polyposis.

The patient has remained perfectly well, and in June 1941 esophagoscopy revealed a somewhat dilated and tortuous tract with only three or four growths, 2 to 3 mm. in size. The esophagram was mainly normal and showed a few translucent areas (fig 5).

## COMMENT

In this patient the recurrent gastrointestinal hemorrhages were due to multiple polyps of the esophagus. The main proof of this pathologic situation rests on the repeated esophagoscopy examinations. The specimen of esophageal tissue secured for biopsy is small and does not reveal a real polyp. The outstanding finding in the microscopic section is the presence of blood vessels in the mucosa itself. Esophageal varices are ruled out by the esophagoscopy description of the polyps, the lack of portal hypertension and the absence of cirrhosis of the liver. The original splenomegaly is hard to explain satisfactorily. Its microscopic appearance is not characteristic of any special disease condition. It may have resulted from the hepatitis occurring in early childhood. Cirrhosis of the liver is ruled out by the absence of hepatic damage and the lack of evidence of portal hypertension either clinically or at operation. Thompson<sup>2</sup> and the members of the Spleen Clinic at Presbyterian Hospital, New York, have shown that congestive splenomegaly does occur in some children without cirrhosis of the liver and is due to stenosis of the portal vein from a congenital defect. In this group hemorrhage occurs from ruptured esophageal varices despite splenectomy. But in rare instances the stenosis may involve the splenic vein alone, and the patient may be cured by splenectomy. From the description of the operation, this does not seem to have been the situation in this patient.

Multiple polyps of the esophagus are rare, and in only 1 case in the literature, to our knowledge, has this condition been complicated by hemorrhages. In 1931 Ginsburg<sup>3</sup> reviewed this subject. He reported a case of his own and described a case reported by Patterson and another reported by Kernan. Hunt<sup>4</sup> reported a case of multiple polyps of the esophagus in 1937. In all these cases the patients complained of dysphagia, and in none of them was the disorder complicated by hemorrhage.

Even in the reported cases of solitary hemangioma<sup>5</sup> of the esophagus the condition has not been complicated by hemorrhage. In 1922 Timbal<sup>6</sup> described a case of multiple polyps of the esophagus in which the patient

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2. Thompson, W. P.: The Pathogenesis of Banti's Disease, *Ann. Int. Med.* **14**:255 (Aug.) 1940.

3. Ginsburg, L.: Multiple Papillomas of Esophagus: Report of Case, *Arch. Otolaryng.* **14**:570 (Nov.) 1931.

4. Hunt, W. M.: Multiple Papilloma of Esophagus: Case Report, *Ann. Otol., Rhin. & Laryng.* **46**:752 (Sept.) 1937.

5. Vinson, P. P.; Moore, A. B., and Bowing, H. H.: Hemangioma of the Esophagus: Report of a Case, *Am. J. M. Sc.* **172**:416 (Sept.) 1926. Broders, A. C.; Vinson, P. P., and Davis, P. L.: Hemangio-Endothelioma of Esophagus: Report of Case, *Arch. Otolaryng.* **18**:168 (Aug.) 1933.

6. Timbal, L.: Tumeurs multiples de l'œsophage, *Arch. d. mal. de l'app. digestif* **12**:126, 1922.

suffered hemorrhages as a complication. According to this report, dysphagia developed in a young man aged 25 and several months later he suffered a severe hemorrhage from the esophagus. Subsequent roentgen and esophagoscopy investigation revealed a polyp in the upper portion of the esophagus and another one in the cardiac portion. The patient spontaneously expelled the upper polyp in a vomiting spell. Severe necrosis in the specimen prevented a definite microscopic diagnosis, but the findings were suggestive of a sarcomatous polyp. The polyp at the cardiac end of the esophagus progressed rapidly in size and finally produced such severe obstruction that a gastrostomy was necessary. Hemorrhages from the polyp recurred, and the patient died of hypostatic pneumonia. An autopsy was not performed. From the rather rapid clinical course and from comparison of the specimen with laryngeal pedunculated tumors, the author concluded that the patient had suffered from sarcomatous polyps of the esophagus.

Instances of multiple tumors of the gastrointestinal tract, complicated at times by hemorrhage, were reported by Bennecke<sup>7</sup> in 1906. He described numerous submucous cavernomas in the gastrointestinal tract of a man aged 52 who died of meningitis. The intestine from the duodenum to the rectum showed numerous nodules varying from pin-head to large bean size. They looked like varicose enlargements. The esophagus and the stomach had similar nodules. They were submucous in location, and while they were less numerous than in the intestine, they were larger. Microscopic examination demonstrated that the condition was due to enlargement of the submucous veins similar to the congenital deformity noted in cavernoma of the liver. Bennecke called the condition cavernous phlebectasia. He stated that 20 cases of similar abnormality had been described in the literature, and while in most of them the condition was asymptomatic, he referred to a report describing fatal internal hemorrhage in 2 children suffering from the condition.

The differentiation of esophageal polyps from esophageal varices by roentgen study of the esophagus after the instillation of barium sulfate is difficult. Buckstein<sup>8</sup> stated:

The essential finding in the roentgen demonstration of esophageal varices is therefore the presence of rounded translucent areas, bead-like in appearance and involving usually the distal portion of the esophagus. There may be momentary variation in the appearance of these areas primarily as a result of peristaltic activity.

Polyps also appear as translucent areas in the lumen of the esophagus on roentgen study after the instillation of barium sulfate, and they are

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7. Bennecke, H.: Ueber kavernöse Phlebektasien des Verdauungstraktus, *Virchows Arch. f. path. Anat.* **184**:171, 1906.

8. Buckstein, J.: *Clinical Roentgenology of the Alimentary Tract*, Philadelphia, W. B. Saunders Company, 1940, p. 60.

more prominent in the lower portion of the esophagus. No variation in the appearance of the translucent areas in the different roentgenograms was noted in the esophageal roentgen studies of the polyps in our case. This might be used as a point in the differential diagnosis of esophageal polyps and esophageal varices by roentgen study.

#### SUMMARY

A case is reported of massive recurrent hematemesis of five years' duration in a girl of 15. The condition apparently began as hepatitis with splenomegaly and was temporarily controlled by splenectomy. Although the liver showed no evidence of permanent damage and there was no increase in portal pressure, the hemorrhages recurred. Esophagoscopy ultimately revealed the presence of multiple polyps, which were removed by fulguration, with the recovery of the patient.

The small specimen obtained for biopsy, the taking of which was complicated by a severe hemorrhage, was unusual in that it presented numerous blood spaces in the thickened squamous epithelium.

In a review of the literature there was found but 1 other instance of hematemesis due to esophageal polyps.



# Progress in Internal Medicine

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## INFECTIOUS DISEASES

A REVIEW OF SIGNIFICANT PUBLICATIONS IN  
1941-1942

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The disruptive effects of the war on scientific study will soon be evident in the amount, quality and character of contributions dealing with infectious disease. Far-reaching changes in viewpoint and interests are also bound to occur incident to the transportation of troops to remote places of the earth, each with their special variety of infections in addition to the usual ones. Medical officers going to tropical regions will be obliged to familiarize themselves with infectious diseases which occur more commonly there, such as malaria, the dysenteries, yellow fever, dengue, cholera, melioidosis, protozoal and metazoal diseases, and the discomforts and dangers of various insect bites. Likewise, numerous other diseases will be encountered, particularly smallpox, tetanus, plague, typhus fever, kala-azar and relapsing fever, most of which the average physician in the United States has never seen.

Physicians who remain at home will have to learn to recognize and treat many of these infections in returned troops who have them either in active or in chronic form or who may be healthy carriers in whom the disease may develop or relapse after months or years of latency. In any event, it may be predicted that interest in exotic diseases will increase and many more contributions concerning them will begin to appear in the literature.

Aside from the exotic infections, epidemics of influenza, meningitis, typhus, dysentery, typhoid, the acute exanthems, mumps, venereal diseases and other infections will no doubt occur among large troop concentrations and especially among civilian populations harassed by poverty, vermin, hardship and starvation. Typhus is indeed already active in many parts of Europe, especially in the endemic centers in southeastern Europe and Spain and even in Germany among Russian prisoners of war.

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From the Jefferson Medical College Hospital.

## CHEMOTHERAPY

Chemotherapy with sulfanilamide and various derivatives was again the subject of many papers published during the year. No strikingly new facts or changes in opinion are evident, but it seems that the usual wave of overenthusiasm incident to the use of new remedies has passed and that the stage of realism has arrived. Numerous controlled studies have confirmed the value of some of the compounds in treating diseases like pneumococcic pneumonia, which need not be reviewed here; others leave the value of chemotherapy of certain infections doubtful, and still others report no beneficial effects at all in the treatment of the diseases studied.

*Pneumococcic Empyema*.—A summary<sup>1</sup> of recent publications shows that the incidence of empyema after pneumococcic lobar pneumonia has been reduced from 5 to about 1 per cent since the advent of therapy with sulfanilamide and various derivatives. Although the incidence is less, when empyema does occur after pneumonia in which treatment is with this type of compound it is apt to be atypical and more difficult to cure. Once the pneumonia has been controlled, such therapy should be discontinued even when pus has accumulated, since continued therapy is useless. Surgical drainage is necessary.

*Subacute Bacterial Endocarditis*.—Almost all reports on this disease reflect pessimism over the results obtained with the chemotherapeutic methods used at present. Willius,<sup>2</sup> for example, finds but little convincing evidence to increase one's optimism. Many reported cures he believes occurred in cases of doubtful or unproved disease. Similar views are expressed by Kinsella.<sup>3</sup> An example of the confusion in bacteriologic diagnosis which may arise is illustrated in one report<sup>4</sup> of a cure supposedly obtained in a patient whose infection was most likely caused by, or associated with, alpha hemolytic streptococci, not with *Streptococcus viridans*.<sup>5</sup>

Poston and Orgain<sup>6</sup> studied the bacteriostatic effect of sulfanilamide and various derivatives on twenty-five strains of *Str. viridans*. The

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1. Burford, T. H., and Blades, B.: The Influence of Sulfonamide Therapy on Postpneumonic Empyema Thoracis, *J. A. M. A.* **118**:950-952 (March 21) 1942.

2. Willius, F. A.: Cardiac Clinics: A Talk on the Hapless Therapy of Subacute Bacterial Endocarditis, *Proc. Staff Meet., Mayo Clin.* **17**:216-218 (April 8) 1942.

3. Kinsella, R. A.: Chemotherapy of Bacterial Endocarditis, *Ann. Int. Med.* **15**:982-986 (Dec.) 1941.

4. Moore, G. B., and Tannenbaum, A. J.: *Streptococcus Viridans* Septicemia: A Cure with Sulfapyridine, *J. A. M. A.* **118**:372-373 (Jan. 31) 1942.

5. Nye, R. N.: *Streptococcus Viridans* Septicemia, Correspondence, *J. A. M. A.* **118**:917 (May 14) 1942.

6. Poston, M. A., and Orgain, E. S.: Comparison of the Bacteriostatic Effect of the Sulfonamide Drugs upon the Growth of Twenty-Five Strains of *Streptococcus Viridans*, *Am. J. M. Sc.* **203**:577-580 (April) 1942.

growth of most strains was inhibited by the drugs in vitro; that of three was inhibited to a considerable extent, and seven strains were not affected at all. The study indicates that different strains vary greatly in their susceptibility to the compounds used.

A few clinicians still advocate further trial with combination therapy using heparin and sulfanilamide or one of its derivatives,<sup>7</sup> but others<sup>8</sup> feel that heparin should no longer be used according to the technic originally advised. General opinion<sup>9</sup> seems to favor further experimental therapy with sulfanilamide and its derivatives now in use and continuation of the trial of newly synthesized compounds in the hope that an efficient one will be found.

Osgood<sup>9a</sup> reports favorable results in the treatment of subacute bacterial endocarditis with neoarsphenamine.

*Staphylococcic Infections.*—Torrey, Julianelle and McNamee<sup>10</sup> question the high degree of success reported by others in the chemotherapy of staphylococcic septicemia. In many cases of "cure" it is possible that staphylococci were transient and innocuous in the circulation. While in certain cases chemotherapy may be helpful in controlling the infection, it is not, the authors believe, strikingly helpful in the majority of cases of genuine staphylococcic septicemia. In their own series of cases, in which treatment was with sulfanilamide and some of its derivatives, the mortality rate was 67 per cent, or about the same as in many previously reported cases in which such compounds were not used.

In treating staphylococcic osteomyelitis Hoyt and his associates<sup>11</sup> obtained better results with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) therapy alone than with surgical treatment in addition.

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7. Leech, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis: Further Experiences, *J. A. M. A.* **117**:1345-1350 (Oct. 18) 1941.

8. MacLean, J.; Meyer, B. B. M., and Griffith, J. B.: Heparin in Subacute Bacterial Endocarditis: Report of Case and Critical Review of Situation, *J. A. M. A.* **117**:1870-1875 (Nov. 29) 1941.

9. Heyer, H. E., and Hick, F. K.: Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfanilamide, Sulfapyridine, and Sulfathiazole: A Review of Previously Reported Treated Cases Including One Cure and One Aborted Case, *Ann. Int. Med.* **15**:291-303 (Aug.) 1941. Field, H.; Hoobler, S. W., and Avery, N. L.: Results of Chemotherapy in Subacute Bacterial Endocarditis, *Am. J. M. Sc.* **302**:798-803 (Dec.) 1941.

9a. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections with a Method of Administration to Maintain Uniform Blood Levels for the Treatment of Serious Staphylococcic Infections and Subacute Bacterial Endocarditis, *Arch. Int. Med.* **69**:746-763 (May) 1942.

10. Torrey, R. G.; Julianelle, L. A., and McNamee, H. G.: The Sulfonamide Therapy of Staphylococcal Septicemia, *Ann. Int. Med.* **15**:431-445 (Sept.) 1941.

11. Hoyt, W. A.; Davis, A. E., and Van Buren, G.: Acute Hematogenous Staphylococcic Osteomyelitis: Treatment with Sulfathiazole Without Operation, *J. A. M. A.* **117**:2043-2049 (Dec. 13) 1941.

They cite the dissenting opinion of Melton,<sup>12</sup> who states that sulfathiazole in his experience did not lessen the need for surgical intervention or check the progress of suppuration. Melton<sup>13</sup> also is unenthusiastic about the effects of the drug in the treatment of staphylococcic pulmonary infections. Sulfathiazole failed to cause a significant response in 3 of 4 cases, yet the patient recovered in each case.

Michael<sup>14</sup> reports 5 cases of staphylococcic pneumonia following infection with influenza A virus. In 4 cases treatment was with sulfathiazole, and in 1 case the patient died. The author believes that sulfathiazole is indicated in the treatment, but a perusal of evidence given in his charts is not convincing. In 2 cases the drug was given in large doses for six days, without influence on the course of the disease. In both cases, the drug was stopped and improvement occurred later. In 1933 I reported 6 cases of staphylococcic pneumonia, with recovery in 4 without chemotherapy. Thus far too few cases have been studied with sufficient control to assure one of the value of treatment with sulfanilamide derivatives.

From experimental studies Kolmer and Brown<sup>15</sup> conclude that the results of chemotherapy of staphylococcic infections are still unsatisfactory as compared with the effects obtained in infections caused by hemolytic streptococci or by pneumococci.

*Meningitis.*—The chemotherapy of meningitis caused by meningococci, hemolytic streptococci, pneumococci, influenza bacilli, staphylococci and other organisms has been so recently reviewed by Finland and Dingle<sup>16</sup> that further comment is unnecessary here. They point out the beneficial effects of such treatment obtained in most cases of infection caused by these bacteria. They show, however, the disappointing truth that the curative effects of chemotherapy of pneumococcic meningitis are not as good as many reports seem to indicate. The present mortality rate in cases in which chemotherapy is employed is nearer to 80 per cent than 35 per cent, as previously claimed.

*Scarlet Fever.*—Top and Young<sup>17</sup> found but little difference in the results of treatment of scarlet fever with sulfanilamide, convalescent

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12. Melton, G.: Sulfathiazole in Treatment of Staphylococcal Infections, *Lancet* **1**:274-278 (March 1) 1941.

13. Melton, G.: Sulphathiazole in Staphylococcal Lung Infection, *Lancet* **2**: 522-523 (Nov. 1) 1941.

14. Michael, M.: Staphylococcus Aureus Pneumonia, with Special Reference to Its Occurrence as a Complication of Influenza, *J. A. M. A.* **118**:869-874 (March 14) 1942.

15. Kolmer, J. A., and Brown, H.: Chemotherapy and Chemoserotherapy of Staphylococcic Infections, *Arch. Int. Med.* **69**:636-646 (April) 1942.

16. Finland, M., and Dingle, J. H.: Treatment of Meningitis, *New England J. Med.* **225**:825-832 (Nov. 20) 1941.

serum or antitoxin. Both serum and antitoxin gave slightly better results than sulfanilamide.

*Rheumatic Fever.*—In opposition to two previous favorable reports Stowell and Button<sup>18</sup> do not recommend the use of small doses of sulfanilamide given over long periods to prevent infections with hemolytic streptococci, which so often precede an attack of rheumatic fever. In about half the children they treated signs of toxicity developed. To be of consistent value the drug would have to be given annually during the winter months until the patient is 17 or 18 years of age.

Hopkins<sup>18a</sup> failed to obtain any beneficial effects in the treatment with sulfanilamide or sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) of 12 patients with rheumatic fever and 49 with streptococcic tonsillitis. Streptococcic tonsillitis developed in 2 patients undergoing intensive treatment with sulfapyridine.

*Bacillary Dysentery and Typhoid Fever.*—Favorable reports continue to appear on the treatment with sulfaguanidine (sulfanilylguanidine) of patients with acute bacillary dysentery and of carriers of dysentery bacilli. Anderson and Cruickshank<sup>19</sup> report good clinical results and a diminution of the convalescent carrier rate. Hardy and his associates<sup>20</sup> had excellent results in the treatment of infection caused by the Flexner, the Newcastle and the Shiga type of bacillus. The carrier state seldom exceeded five days. Sulfaguanidine, contrary to other previous and less favorable reports, proved of value in ridding carriers of the bacilli and may serve as an important epidemiologic measure in this respect. Rantz and Kirby<sup>21</sup> rid 9 of 11 carriers of bacilli, and in the 2 instances of failure the organisms were not typical Flexner bacilli. In one study<sup>22</sup> on chil-

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17. Top, F. H., and Young, D. C.: The Treatment of Moderately Severe Scarlet Fever: A Study of Alternate Patients Treated with Sulfanilamide, Convalescent Serum and Scarlet Fever Antitoxin, *J. A. M. A.* **117**:2056-2060 (Dec. 13) 1941.

18. Stowell, D. D., and Button, W. N.: Observations on the Prophylactic Use of Sulfanilamide on Rheumatic Patients with Report of One Death, *J. A. M. A.* **117**:2164-2166 (Dec. 20) 1941.

18a. Hopkins, W. A.: Use of Sulfonamide Group of Drugs in Treatment of Tonsillitis Due to Beta Hemolytic Streptococcus and in Acute Rheumatic Fever, *Ann. Rheumatic Dis.* **2**:233-247 (Dec.) 1941.

19. Anderson, D. E. W., and Cruickshank, R.: Treatment of Bacillary (Flexner) Dysentery with Sulfanilylguanidine, *Brit. M. J.* **2**:497-500 (Oct. 11) 1941.

20. Hardy, A. V.; Watt, J., and Peterson, J.: Studies of the Acute Diarrheal Diseases: VIII. Sulfaguanidine in the Control of Shigella Dysenteriae Infections, *Pub. Health Rep.* **57**:529-535 (April 10) 1942.

21. Rantz, L. A., and Kirby, W. M. M.: Sulfaguanidine in the Treatment of Dysentery Carriers, *J. A. M. A.* **118**:1268-1271 (April 11) 1942.

22. Cooper, M. L.; Zucker, R. L., and Wagoner, S.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children, *J. A. M. A.* **118**:1520-1523 (Nov. 1) 1941.

dren with acute diarrheal disease sulfathiazole was used with success in treating those whose stools contained Flexner and Sonne dysentery bacilli but not in treating the rest. The drug was also effective in preventing the carrier state in convalescent patients.

Sulfaguanidine was used effectively in clearing a colony of mice of most carriers of an enzootic *Salmonella* infection.<sup>23</sup>

Hall<sup>24</sup> had no success in treating 20 patients with typhoid fever. Sulfaguanidine did not decrease the duration or the intensity of the disease or clear the stool of typhoid bacilli. The same number of complications occurred as in 20 untreated patients. Similar results were reported by Watt and Peterson.<sup>24a</sup> Cutting and Robson<sup>25</sup> state that there is no dependable or efficient curative drug for treating typhoid carriers. Six carriers studied by them were not cured by treatment with hydroxyphenothiazone (thionol), phenothiazine, soluble iodophthalein, sulfaguanidine or sulfadiazine (2-[paraaminobenzene-sulfonamido]-pyrimidine). Cholecystectomy also fails in a considerable number of cases. Similar results were reported by another group of investigators.<sup>26</sup> Sulfaguanidine failed to eliminate typhoid bacilli from the stool in 5 carriers. Oral treatment with soluble iodophthalein in 65 cases in which typhoid bacilli were present in the bile rendered the bile sterile in 32 per cent but freed the stool from the bacilli in only 8 per cent.

*Cholera.*—According to Griffiths,<sup>26a</sup> sulfathiazole, sulfadiazine and sulfanilamide inhibited the growth of *Vibrio cholerae* in vitro. Sulfathiazole, sulfadiazine, succinylsulfathiazole and sulfaguanidine given intragastrically were effective in the treatment of mice experimentally infected with *V. cholerae*.

A group<sup>27</sup> from the Mayo Clinic gives an unenthusiastic report of sulfaguanidine treatment of various types of chronic ulcerative colitis

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23. Beamer, P. R.: Sulfanilylguanidine in Control of *Salmonella* Infection and Carrier State in Mice, *Proc. Soc. Exper. Biol. & Med.* **49**:418-421 (March) 1942.

24. Hall, W. M.: Use of Sulfaguanidine in a Controlled Series of Typhoid Cases, *New Orleans M. & S. J.* **94**:283-284 (Dec.) 1941.

24a. Watt, J., and Peterson, J. S.: Sulfaguanidine Noneffective in the Treatment of Typhoid Fever and Typhoid Carriers, *Pub. Health Rep.* **57**:872-873 (June 5) 1942.

25. Cutting, W. C., and Robson, G. B.: The Alleged Efficiency of Medicinal Treatment of Typhoid Carriers, *J. A. M. A.* **118**:1447-1449 (April 25) 1942.

26. Saphir, W.; Baer, W. H., and Plotke, F.: The Typhoid Carrier Problem, *J. A. M. A.* **118**:964-967 (March 21) 1942.

26a. Griffiths, J. J.: Laboratory Studies of the Effect of Sulfonamide Drugs on *V. Cholerae*, *Pub. Health Rep.* **57**:814-818 (May 29) 1942.

27. Stickney, J. M.; Heilman, F. R.; Barga, J. A., and Dearing, W. N.: Sulfaguanidine in Ulcerative Intestinal Disease, *Proc. Staff Meet., Mayo Clin.* **17**:33-44 (Jan. 21) 1942.

not due to *Endamoeba histolytica*, *Mycobacterium tuberculosis* or the virus of lymphogranuloma venereum. While "many" patients apparently were helped by sulfaguanidine, the authors conclude that the place of the drug in the treatment of ulcerative intestinal disease has not been established but that its value in the therapy of some intestinal diseases "seems definite."

As may be expected, attempts are being made to synthesize a compound better than sulfaguanidine for the treatment of intestinal infections. In testing a number of drugs Poth and Knotts<sup>28</sup> found that succinylsulfanilamide and succinylsulfathiazole were effective experimentally. The latter drug was tested in a number of patients with various intestinal diseases. In 95 of 100 cases the intestinal flora, particularly of colon bacilli, was greatly altered.

*Virus Diseases.*—Sulfanilamide and some of its derivatives had no influence on experimental infection with vaccinia, smallpox<sup>29</sup> or western equine encephalomyelitis.<sup>30</sup> Although chemotherapy apparently prevented death of animals infected with the virus of lymphogranuloma venereum,<sup>31</sup> the effects were not always curative. Similar results were obtained by Rodaniche.<sup>32</sup> Chemotherapy influenced the disease in mice favorably, but the virus persisted in the brain. Because of the apparent effect of the drugs on the virus of lymphogranuloma venereum, Rake, Jones and Nigg<sup>33</sup> tested chemotherapeutic agents on the related viruses of mouse pneumonitis and meningopneumonitis. The effect of chemotherapy on the viruses of lymphogranuloma venereum and mouse pneumonitis, in addition to their apparent particulate nature, suggests to the authors that these infectious agents and also the one causing psittacosis are not true viruses.

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28. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, *Arch. Surg.* **44**:208-222 (Feb.) 1942.

29. Kolmer, J. A., and Brown, H.: Failure of Sulfanilamide in Treatment of Experimental Vaccinia Rabbits, *Proc. Soc. Exper. Biol. & Med.* **48**:138-140 (Oct.) 1941.

30. Schlattbauer, C. F.: Treatment of Equine Encephalomyelitis (Western) with Certain Sulfonamide Compounds: An Experimental Study, *Proc. Staff Meet., Mayo Clin.* **17**:187-189 (March 25) 1942.

31. Jones, H. P.; Rake, G., and McKee, C. M.: Chemotherapy of Lymphogranuloma Venereum with Sulfonamide Drugs, *Proc. Soc. Exper. Biol. & Med.* **48**:318-323 (Oct.) 1941.

32. Rodaniche, E. C.: Sulfanilylguanidine and Sulfanilamide in the Treatment of Lymphogranuloma Venereum Infection of Mice, *J. Infect. Dis.* **70**:58-61 (Jan.-Feb.) 1942.

33. Rake, G.; Jones, H., and Nigg, C.: Sulfonamide Chemotherapy of Mouse Pneumonitis, Meningopneumonitis and Lymphogranuloma Venereum, *Proc. Soc. Exper. Biol. & Med.* **49**:449-452 (March) 1942.

*Miscellaneous Infections.*—In cases of filariasis<sup>35</sup> sulfapyridine controlled lymphadenitis which was probably caused by secondary streptococcic infection but had no effect on the filarias in the blood stream. Sulfadiazine had a beneficial effect in reducing the number of *Haemophilus pertussis* organisms in inoculated mice.<sup>36</sup> Hinshaw and Feldman<sup>37</sup> present further evidence of the favorable effect of sodium p, p' - diaminodiphenylsulfone - N, N' - didextrosulfonate (promin) on experimental tuberculosis in guinea pigs. All of the untreated control animals died, while 84 per cent of 80 treated animals remained well. Coggeshall, Maier and Best<sup>38</sup> used this compound and sulfadiazine in the treatment of malaria in human beings caused by *Plasmodium vivax* and by *Plasmodium falciparum* and obtained definite curative effects in most cases. It appears, therefore, that compounds unrelated to quinine or atabrine may be valuable antimalarial agents, but they should at present only be regarded as substitutes and not used in preference to older drugs.

Sulfathiazole seemed to be of benefit in the treatment of 7 patients with infectious mononucleosis,<sup>39</sup> but the number tested is too small to convince one of its value.

*Untoward Effects.*—In discussing the advantages of any form of treatment it is always necessary to consider its harmful effects as well. A number of newly recognized untoward effects have been reported, some in experimental animals and others in patients. For example, sulfaguanidine caused extensive hyaline sclerosis and calcification of blood vessels in young rats.<sup>40</sup> In other experiments with rats the drug caused

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34. Deleted by author.

35. Earle, K. V.: Sulfapyridine in Filariasis: Further Experiences, *Lancet* **2**: 667-668 (Nov. 29) 1941.

36. Hornibrook, J. W.: Sulfadiazine in Murine Pertussis, *Pub. Health Rep.* **57**:535-537 (April 10) 1942.

37. Hinshaw, H. C., and Feldman, W. A.: Treatment of Experimental Tuberculosis: Use of Sodium P, P'-Diaminophenylsulfone-N, N'-Didextrose Sulfonate ("Promin") with Notes on Some Toxic Effects Observed in Man, *J. A. M. A.* **117**:1066-1068 (Sept. 27) 1941.

38. Coggeshall, L. T.; Maier, J., and Best, C. A.: The Effectiveness of Two New Types of Chemotherapeutic Agents in Malaria, *J. A. M. A.* **117**:1077-1081 (Sept. 27) 1941.

39. Hoffman, H. T.; Lees, H. D., and Comroe, B. I.: Use of Sulfathiazole in Infectious Mononucleosis, *Am. J. M. Sc.* **203**:731-736 (May) 1942.

40. Daft, F. S.; Spicer, S. S., and Sebrell, W. H.: The Occurrence of Hyaline Sclerosis and Calcification of Blood Vessels in Rats on Sulfaguanidine, *Pub. Health Rep.* **57**:217-218 (Feb. 13) 1942.



hypertrophy and hyperemia of the thyroid.<sup>41</sup> French and Weller<sup>42</sup> noted interstitial myocarditis in patients in whom the sole common factor was the use of sulfanilamide compounds. Similar lesions were caused experimentally in animals.

In one study<sup>43</sup> while "drug-fever" developed in only 5 per cent of sulfathiazole-treated patients after the seventh day of therapy, 36 per cent had fever if the course of treatment was repeated and 80 per cent of those who had fever after the second course also had fever after a third course. The authors therefore justly advise the use of sulfathiazole for the more serious infections only.

Although recent experience in Hawaii in the treatment of war wounds with sulfanilamide or one of its derivatives was highly satisfactory, it must be remembered that in contrast with injuries received during trench warfare, these wounds were undoubtedly cleaner. No doubt local chemotherapy will be of value even in grossly contaminated wounds, but final evaluation is not yet possible. Bick<sup>44</sup> points out that sulfanilamide or sulfathiazole applied to wounds of soft tissue and to clean surgical incisions delays healing by about 50 per cent and promotes scarring. They must be used, nevertheless, in contaminated wounds and even when soiling is anticipated.

Taylor<sup>45</sup> advises against stuffing a "sulfonamide compound" into "every cavity, scratch, wound or orifice" on the grounds that "all sulfonamides in common use" are irritant drugs which at times may themselves cause abscess formation and peritoneal adhesions. The practice of using these chemicals in clean wounds, including appendectomy wounds, is questionable.

*Drug Fastness.*—According to certain experiments,<sup>46</sup> gonococci become sulfanilamide "fast" or sulfapyridine (2-[paraaminobenzene-sulfonamido]-pyridine) "fast" relatively easily, but little, if any, tolerance for sulfathiazole develops in a test tube. In this respect the gonococcus seems to differ from the pneumococcus, which when it becomes drug fast to one compound is also drug fast to others.

41. Mackenzie, J. B.; Mackenzie, C. G., and McCollum, E. V.: The Effect of Sulfanilylguanidine on the Thyroid of the Rat, *Science* **94**:518-519 (Nov. 28) 1941.

42. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, *Am. J. Path.* **18**:109-118 (Jan.) 1942.

43. Lyons, R. H., and Balberor, H.: Febrile Reactions Accompanying the Readministration of Sulfathiazole, *J. A. M. A.* **118**:955-958 (March 21) 1942.

44. Bick, E. M.: Observations on the Topical Use of Sulfonamide Derivatives, *J. A. M. A.* **118**:511-513 (Feb. 14) 1942.

45. Taylor, F. W.: The Misuse of Sulfonamide Compounds, *J. A. M. A.* **118**:959-961 (March 21) 1942.

46. Carpenter, C. M.; Charles, R., and Allison, S. D.: Effect of Gradually Increased Concentrations of Sulfathiazole on the Gonococcus in Vitro, *Proc. Soc. Exper. Biol. & Med.* **48**:476-478 (Nov.) 1941.

Resistance to sulfanilamide may also develop in hemolytic streptococci, according to the study of Hendry.<sup>47</sup> The acquired drug fastness of the strain studied was unchanged after fourteen subsequent passages in mice.

According to one group of workers,<sup>48</sup> sulfanilamide and various derivatives have no particular specificity in vitro for different bacteria. By using a special ratio involving paraaminobenzoic acid, each of the six compounds tested was equally effective in inhibiting growth of a variety of bacteria. The authors' views are supported by some observers who noted no particular difference in the effect of sulfapyridine, sulfathiazole or sulfadiazine in the treatment of pneumococcic pneumonia, except, of course, in the difference of the toxic effects of the drugs on patients.

#### COCCIC DISEASES

*Pneumococcic Pneumonia.*—O'Hara<sup>49</sup> calls attention, as I did in the annual review for 1940,<sup>50</sup> to the steady decline in the death rate of pneumonia since 1900. No specific antipneumococcic measures can be credited for this favorable trend, which is also present in mortality statistics of other infectious diseases. He believes, as I do, that the decline in mortality has been brought about by many complex factors, including better housing and better nutrition. It is interesting to speculate on the possible effect on the mortality curve had sulfanilamide derivatives been introduced fifteen or twenty years ago. The striking further reduction in mortality rate since 1938 can be unquestionably attributed for the most part to chemotherapy.

The results of a statistical study<sup>51</sup> indicate that the death rate from pneumonia in 1940 was about 10 per hundred thousand insurance policy holders. It is possible that this low rate may be near the minimum, below which it is unlikely that mortality can be reduced. Of the policy holders dying from pneumonia, 84 per cent had had chemotherapy, 73 per cent without additional serum and only 11 per cent with serum. Less than 1 per cent had received serum alone. Of the 464 cases of pneumonia in which bacteriologic study was done, infection was pneumococcic in origin in 72 per cent, streptococcic in 5.6 per cent and staphylo-

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47. Hendry, J.: A Study of Hemolytic Streptococci from a Horse Treated with Sulfanilamide After Streptococcal Bacteremia Developed During Immunization, *J. Infect. Dis.* **70**:112-118 (March-April) 1942.

48. Wyss, O.; Grubaugh, K. K., and Schmelkes, F. C.: Non-Specificity of Sulfonamides, *Proc. Soc. Exper. Biol. & Med.* **49**:618-621 (April) 1942.

49. O'Hara, D.: Pneumonia in Massachusetts: 1900-1940, *New England J. Med.* **225**:402-404 (Sept. 11) 1941.

50. Reimann, H. A.: Infectious Diseases: A Review of Significant Publications in 1939-1940, *Arch. Int. Med.* **66**:478-525 (Aug.) 1940.

51. Some Current Results in Pneumonia Treatment, *Statist. Bull. Metrop. Life Insur. Co.* **22**:1-4 (Oct.) 1941.

coccic in 2.2 per cent; the causative organism was not identified in the others. In the series of cases studied apparently no attempt was made to type the pneumococcus supposedly involved in one fourth of the cases, against the advice of many authorities who properly urge that specific etiologic diagnoses still be made in all cases.

In reading papers one must not be misled by statements<sup>52</sup> apparently reflecting uncontrolled personal experience, such as "In the decade following the war, the pneumococcus could rarely be found" in pneumonia or "During the past decade, pneumococci again have been demonstrated with increasing frequency." Nor is there any evidence aside from increasing recognition that "the so-called virus type of pneumonia is increasing in frequency."

In studying the flora in the nasopharynx of children in an orphanage Smillie<sup>53</sup> found type XIV pneumococci to be present in 32 per cent, or ten times the usual expectancy, yet pneumonia did not develop in any of the children. This gives evidence that an invasive type of pneumococcus may be widespread without causing symptoms, unless, as later happened in some cases, mild infection of the respiratory tract makes invasion possible. Of 31 instances of pneumonia, 10 were caused by organisms of type XIV; of 83 patients with a "cold," 30 carried organisms of type XIV, and of 40 healthy children, 10 carried type XIV pneumococci in the throat. There was, therefore, no statistical significance to the prevalence of the pneumococcus in those sick or well in the group studied.

In a study<sup>54</sup> of the problem of types of pneumococci seventeen "new" types in addition to the thirty-two known ones were found. Many are subtypes of established types, but nine are distinctive in themselves. Few of the newly classified types have much virulence for mice.

Mørch,<sup>54a</sup> of Copenhagen, obtained Walter's new types from New York and reclassified them with his own numerical system. He added more new types and subtypes of his own, so that at present sixty-eight separate or slightly different types are included in the complicated pattern. One wonders if the end will ever be reached.

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52. Wood, H. G.: Present Day Treatment of Pneumonia, *Minnesota Med.* **25**:24-27 (Jan.) 1942.

53. Smillie, W. G.: The Epidemiology of Pneumonia: The Role of Type XVI Pneumococci in Producing Illness, *Tr. A. Am. Physicians* **56**:129-138, 1941.

54. Walter, A. W.; Guevin, V. H.; Beattie, M. V.; Cotler, H. Y., and Bucca, H. B.: Extension of Separation of Types Among the Pneumococci: Description of Seventeen Types in Addition to Types 1 to 32 (Cooper) with Recommendation for Terminology of All Types Reported Through 1940, *J. Immunol.* **41**:279-294 (July) 1941.

54a. Mørch, E.: Further Studies on the Serology of the Pneumococcus Group, *J. Immunol.* **43**:177-202 (Feb.) 1942.

In extending previous observations Frisch and Price<sup>55</sup> report the value of examination of sputum as a reliable guide in prognosis and therapy in 270 cases. Sputum counts with pneumococci exceeding 50 per oil immersion field indicated potentially overwhelming infection. Chemotherapy was reserved for patients with 11 to 50 or more pneumococci per field, and those patients whose sputum had 10 or fewer organisms per field all recovered without therapy.

In Bigg's<sup>56</sup> experiments on dogs the injection of small amounts of specific soluble substance during experimental pneumococcic pneumonia resulted in overwhelming infection, apparently because of impaired phagocytosis in the pneumonic area and an inability to localize the infection. These experiments confirm earlier ones by Cole and by Robertson regarding the deleterious effect of the capsular substance in neutralizing specific immune bodies in cases of pneumococcic pneumonia.

According to Wooley and Sebrell,<sup>57</sup> mice fed a diet deficient in riboflavin or thiamine were more susceptible to fatal infection with pneumococci than mice fed a complete diet. The daily additional feeding of large amounts of both substances to mice kept on diets deficient in the respective vitamins at the time of inoculation did not reduce the number of animals dying from the infection.

*Other Forms of Pneumonia.*—Michael<sup>14</sup> reports cases of staphylococcic pneumonia, in many of which the pneumonia was preceded by an attack of influenza, which appeared to be an important predisposing factor. Other cases are reported by Gáspár.<sup>58</sup> A good review of pulmonary tularemia, or tularemic pneumonia, with a bibliography and a report of 3 fatal cases was made by Kennedy.<sup>59</sup> Julianelle<sup>60</sup> reviewed the subject of *Bacillus Friedländer* pneumonia. Two cases of pulmonary syphilis, or syphilitic pneumonia, were discussed by Lieu,<sup>61</sup> and the

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55. Frisch, A. W., and Price, A. E.: Sputum Studies in Pneumonia: The Selection of Therapy, *Ann. Int. Med.* **15**:987-993 (Dec.) 1941.

56. Bigg, E.: Influence of Specific Soluble Substance on the Course of Experimental *Pneumococcus* Pneumonia, *Proc. Soc. Exper. Biol. & Med.* **48**:245-247 (Oct.) 1941.

57. Wooley, J. G., and Sebrell, W. H.: Nutritional Deficiency and Infection: I. Influence of Riboflavin or Thiamin Deficiency on Fatal Experimental Pneumococcal Infection in White Mice, *Pub. Health Rep.* **57**:149-161 (Jan.) 1942.

58. Gáspár, I. A.: Study of Primary Staphylococcic Pneumonias Occurring at the Rochester General Hospital, *New York State J. Med.* **41**:834-840 (April 15) 1941.

59. Kennedy, J. A.: Pulmonary Tularemia, *J. A. M. A.* **118**:781-787 (March 7) 1942.

60. Julianelle, L. A.: Pneumonia of *Friedländer's Bacillus*, *Ann. Int. Med.* **15**:190-206 (Aug.) 1941.

61. Lieu, V. T.: Acquired Pulmonary Syphilis: Report of Two Cases with Review of Literature, *Chinese M. J.*, March 1940, supp. 3, pp. 145-157.

pertinent literature was reviewed. Hegglin<sup>62</sup> discussed cases of a peculiar form of infiltration of the lungs, or atypical pneumonia, with positive Wassermann reactions. Two cases of pulmonary histoplasmosis were presented by Meleney.<sup>63</sup>

Doubt has been cast on the existence of so-called "rheumatic pneumonia." Two authors<sup>64</sup> were unable to find Aschoff bodies in the lungs in 45 cases. There were many patches of dark red rubbery areas, but the lesions were composed of the results of vascular damage, as are rheumatic lesions elsewhere. Although the pathologic picture is characteristic, the authors do not believe it represents a specific pulmonary lesion. These conclusions are at variance with several previous publications and my own observations, according to which Aschoff bodies, or bodies closely resembling them, were present in the pulmonary lesions during rheumatic fever.

According to Wolman and Bayard,<sup>65</sup> the nature of the fatty substance in the lung in cases of oil aspiration pneumonia can be determined by the gross appearance of the lesion, by special staining reactions, by histologic changes and by fluorescence of the pulmonary lesion. Tables are included in the paper to assist identification.

"Virus" pneumonia is discussed on page 156.

*Streptococci Infection.*—Boisvert<sup>66</sup> points out how important it is to identify the type of hemolytic streptococcus causing disease in order to determine the source of an epidemic and to control it. In many cases he believes failure to determine the type by the Griffith slide-agglutination technic may be due to the prozone phenomenon, which may be overcome by diluting the typing serum sometimes as much as 1:80.

Rantz<sup>67</sup> reviews the literature on the typing of hemolytic streptococci of the Lancefield group A. There are no types especially responsible for scarlet fever. Types 1, 2, 3 and 4 are perhaps more frequent causes than other types. Even in a local epidemic several types may be prevalent, and as in the case of meningococci, the prevalence of certain types in a community changes from year to year. Hemolytic streptococci are often found in the throats of healthy persons, but their type fre-

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62. Swiss Society for Internal Medicine, Foreign Letters (Switzerland), J. A. M. A. **117**:1111 (Sept. 27) 1941.

63. Meleney, H. E.: Pulmonary Histoplasmosis: Report of Two Cases, Am. Rev. Tuberc. **44**:240-247 (Aug.) 1941.

64. Epstein, E. L., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074-1094 (Dec.) 1941.

65. Wolman, I. J., and Bayard, A. B.: Experimental Aspiration Pneumonia: Fluorescence and Pathology, Am. J. M. Sc. **202**:542-553 (Oct.) 1941.

66. Boisvert, P. L.: The Typing of Hemolytic Streptococci, Science **94**:193-194 (Aug. 22) 1941.

67. Rantz, L. A.: The Serological Typing of Hemolytic Streptococci of the Lancefield Group A, J. Clin. Investigation **21**:217-227 (March) 1942.

quency is not correlated with the types causing scarlet fever in the same season, and the same type may cause both scarlet fever and tonsillitis. According to various reports, however, the types causing scarlet fever and those causing surgical infections are often different, and postscarlatinal complications are usually caused by types other than those responsible for the scarlet fever. Nevertheless, according to Rantz's own studies, and as one would expect, the type distribution of strains from various sources is similar whether they cause otitis media or surgical infections or are from excised tonsils. All types appear to be similarly affected by sulfanilamide and various derivatives. By the use of his technic for typing, 80 to 95 per cent of strains could be classified.

Touroff<sup>68</sup> made an interesting observation during operation on a patient with patent ductus arteriosus and subacute bacterial endocarditis. Cultures made simultaneously of blood from the pulmonary artery and blood from the aorta showed fewer colonies of *Str. viridans* in the blood returning from the lungs. This provides further evidence that the lungs have an important role in filtering bacteria from the circulation.

*Staphylococcic Infection.*—As discussed in the section on chemotherapy, staphylococcic infections do not respond to chemotherapy as well as infections caused by other organisms; therefore attempts at specific therapy are active along other lines as well. Julianelle<sup>69</sup> reports further studies with the use of type A antiserum. Although in many cases in which treatment is with this agent the effects may result from nonspecific factors, there is evidence, he feels, of the participation of the type-specific anticarbohydrate factor. Serum therapy and surgical drainage are both necessary because of the inability of the serum to control localized lesions. The actual evaluation of antiserum, however, must await future trial.

The results of studies<sup>70</sup> on experimental bacteriophage therapy do not support the use of this substance in the treatment of staphylococcic infections. In some cases it was actually harmful.

Spink and Vivino<sup>71</sup> find that the coagulase test is the simplest and most reliable method for differentiating pathogenic from nonpathogenic

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68. Touroff, A. S. W.: Blood Cultures from Pulmonary Artery and Aorta in Patients with Infected Patent Ductus Arteriosus, *Proc. Soc. Exper. Biol. & Med.* **49**:568-569 (April) 1942.

69. Julianelle, L. A.: Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia: Second Report, *Ann. Int. Med.* **16**:303-326 (Feb.) 1942.

70. Sulkin, S. C.; Douglass, D. D., and Bronfenbrenner, J.: Bacteriophage Therapy: IV. Effect of Bacteriophage in Experimental Staphylococcal Septicemia in Rabbits, *J. Infect. Dis.* **70**:92-95 (Jan.-Feb.) 1942.

71. Spink, W. W., and Vivino, J. J.: The Coagulase Test for Staphylococci and Its Correlation with the Resistance of the Organisms to the Bactericidal Action of Human Blood, *J. Clin. Investigation* **21**:353-356 (May) 1942.

staphylococci. Strains giving a positive reaction resist the bactericidal action of blood and are pathogenic, but even strains which give negative reactions and which are ordinarily harmless may on occasion be pathogenic and result in fatal infection. Strains giving positive reactions may yield negative reactions on subculture, and the reverse may occur, probably through the mechanism of bacterial dissociation.

*Meningococci.*—Branham and Carlin <sup>72</sup> recall how the types of meningococci in a population change from time to time. In 1936, for example, 90 per cent of strains were of group I. In 1937 group II strains increased to 16 per cent of the total number and in 1938 to 46 per cent. In later studies it appeared that yet another strain appeared which was a distinct immunologic entity but was still related to group II. The new strain comprised about 50 per cent of the strains isolated at the time.

#### BACILLARY DISEASES

*Dysentery.*—Hardy and his associates <sup>73</sup> report excellent results in the use of new mediums for the isolation of dysentery bacilli. They first used desoxycholate-citrate medium and later found Shiga-Salmonella agar even better. The formula of the latter is not given. The full value of either of these selective mediums is obtained when the whole surface is inoculated with the maximum amount of fecal material which will yield isolated colonies. Cultures are best obtained with material procured on rectal swabs.

This technic was applied to samples of stools from a group of 103 patients with dysentery during convalescence. Eighty-two per cent of the patients were found to be carriers. Known convalescent carrier states lasted thirty-four days on the average. In another study, <sup>72b</sup> of a total of over 6,000 persons in the southern states and in Puerto Rico who had had no diarrheal disorder, about 4 per cent were found to carry *Shigella dysenteriae*.

Macumber <sup>74</sup> gives a good résumé of his experience with acute bacillary dysentery in Panama. The Flexner and the Sonne type of dysentery bacillus were responsible for infection in the 263 cases studied. Specific serum therapy did not appear to be helpful.

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72. Branham, S. E., and Carlin, S. A.: Comments on a Newly Recognized Group of the Meningococcus, *Proc. Soc. Exper. Biol. & Med.* **49**:141-144 (Feb.) 1942.

73. (a) Hardy, A. V.; Watt, J., and DeCapito, T. M.: Studies of the Acute Diarrheal Diseases: VI. New Procedures in Bacterial Diagnosis, *Pub. Health Rep.* **57**:521-524 (April 10) 1942. (b) Watt, J.; Hardy, A. V., and DeCapito, T. M.: Studies of the Acute Diarrheal Diseases: VII. Carriers of *Shigella Dysenteriae*, *ibid.* **57**:524-529 (April 10) 1942. (c) Hardy, Watt and Peterson.<sup>20</sup>

74. Macumber, H. H.: Acute Bacillary Dysentery, *Arch. Int. Med.* **69**:624-635 (April) 1942.

An outbreak in an institution of 238 cases of acute gastroenteritis caused by *Salmonella typhi* murium raised several important points.<sup>75</sup> The source was suspected to be roast turkey, and the question was whether the birds were sick before they were killed or whether the meat was contaminated in preparation by carriers, either human or murine. Bacteria may survive and actually multiply in the center of roasted flesh or in dressing which is not heated too much to serve as a good incubator. Carrier states of infected persons may last for many weeks, contrary to previous opinion that the bacilli disappeared quickly after recovery from the disease.

Infections caused by dysentery bacilli spread slowly through a community suggesting person to person infection, while outbreaks caused by *Salmonella* are more explosive and without evidence of contact infection. In the outbreak just referred to the infection disappeared from the community with the termination of convalescent carrier states.

*Typhoid Fever.*—Botsford<sup>76</sup> reports a case of cholecystitis caused by the typhoid bacillus forty-three years after typhoid fever. There had been four intervening attacks of cholecystitis. Although the patient undoubtedly excreted typhoid bacilli in her stool, there is no evidence that she ever caused infection in others.

Whitfield<sup>77</sup> resents the implication that typhoid fever is pandemic in the southern states because of primitive sanitation. The death rate for typhoid in 1940, he points out, is about the same in Mississippi as in Connecticut, even less if only the white race is considered.

*Diphtheria.*—The problem of malignant diphtheria was discussed editorially.<sup>78</sup> Since 1927 a "new" highly fatal form of diphtheria has been encountered in Europe for which the standard prophylactic measures and antitoxin therapy were without value. Bacteriologic studies soon showed that at least three forms, or types, of diphtheria bacilli may cause the disease, namely, the mitis; the intermedius, commonly found in this country, and the gravis, which causes the severest infection. In one European epidemic the gravis type caused 96 per cent of infections. In studies by O'Meara to determine the reason for the failure of antitoxin to influence infection caused by the gravis type it was

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75. Mosher, W. E.; Wheeler, S. M.; Chant, H. L., and Hardy, A. V.: Studies of the Acute Diarrheal Diseases: V. An Outbreak Due to *Salmonella Typhi* Murium, Pub. Health Rep. **56**:2415-2426 (Dec. 19) 1941.

76. Botsford, T. W.: Acute Typhoid Cholecystitis and Cholelithiasis Occurring Forty-Three Years After Typhoid Fever: Report of a Case, New England J. Med. **224**:799-800 (May 8) 1941.

77. Whitfield, R. N.: Typhoid in the South, Correspondence, J. A. M. A. **118**:839 (March 7) 1942.

78. Synergistic Toxins of Diphtheria Gravis, editorial, J. A. M. A. **118**:301-302 (Jan. 24) 1942. Newer Knowledge of Diphtheria Gravis, editorial, *ibid.* **118**:380-381 (Jan. 31) 1942.



found that the mitis form produced an antitoxin effective only against mild infections. The gravis form produces both exotoxin "A" and endotoxin "B," which together constitute the toxin necessary to evoke an antitoxin capable of controlling the infections caused by this form. The "B" factor also appears to serve as a vector for a "spreading factor" analogous to that produced by certain pathogenic cocci. One reason for the failure of commercially prepared antitoxin to influence infections caused by the gravis type seems to be that the anti-"B" component is destroyed in the process of manufacture. It is hoped that the selection of suitable strains and the proper preparation of antitoxin will serve to minimize the threat of this dangerous form of diphtheria. The first infections with *Bacillus diphtheriae gravis* in America appeared in Nova Scotia in 1941 but were promptly checked without evidence of further spread.

*Tetanus.*—A résumé on the treatment of tetanus was published. According to Spaeth,<sup>79</sup> the gross mortality in 96 patients was 35 per cent. No deaths occurred among patients whose temperature remained normal, but 69 per cent of those with fever died. This suggests a possible bearing of the presence of secondary infection in patients who die and of the result of the delayed effects of toxin alone in those who recover. In the author's experience sedative drugs were the keystone of treatment. An average dose of 30,000 American units of antitoxin was given but never intrathecally. He regards treatment of the local lesion as unimportant.

*Gas Bacillus Infection.*—The overly enthusiastic views of several authors concerning the value of roentgen therapy in the treatment of gas bacillus infection provoked timely editorial comment.<sup>80</sup> It is pointed out that many observers consider roentgen therapy ineffective and find no basis whatever for its use in the treatment of infections caused by gas bacilli. Well controlled clinical and experimental studies failed to show any beneficial influence of such treatment.

One author<sup>81</sup> reports 4 instances of infection with gas-producing bacilli in diabetic patients, yet in these cases colon bacilli, not Welch's bacilli, were the cause. The high sugar content of the blood and tissue was thought to favor the growth of these bacteria. It is probable that the matter is not quite so simply explained. Another author<sup>82</sup> reports

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79. Spaeth, R.: Therapy of Tetanus: A Study of Two Hundred and Seventy-Six Cases, *Arch. Int. Med.* **68**:1133-1160 (Dec.) 1941.

80. Roentgen Therapy of Gas Bacillus Infection, editorial, *J. A. M. A.* **118**:230 (Jan. 17) 1942.

81. Gillies, C. L.: Interstitial Emphysema in Diabetes Mellitus Due to Colon Bacillus Infection: Report of Four Cases, *J. A. M. A.* **117**:2240-2242 (Dec. 17) 1941.

82. Leder, H. L.: *Proteus Vulgaris* as Gas Producer in Diabetes, Correspondence, *J. A. M. A.* **118**:664 (Feb. 21) 1942.

the bacillus *Proteus vulgaris* as another bacterium able to produce infection and gas in diabetic patients. These observations emphasize the importance of making etiologic diagnoses. Obviously, infections accompanied with the formation of gas are not all caused by the Welch bacillus and should not be treated as such unless they are.

*Tularemia*.—Francis and Felton<sup>83</sup> were unable to produce protective antibodies against tularemia in the serum of horses, sheep or rabbits, although specific agglutinins developed. No evidence of protective antibody was found in "convalescent" human serum. These studies do not support the use of antitularemia serum in the treatment of the disease.

Ey and Daniels<sup>84</sup> cite an example of a hunter and his 3 dogs who contracted tularemia from wild rabbits. The dogs acquired the infection by ingesting infected rabbit meat and became mildly sick; specific agglutinins developed in their blood.

*Pasteurella tularensis* may occasionally be cultivated directly from the blood of patients on blood-dextrose-cystine agar.<sup>85</sup>

*Plague*.—Although discussed previously, particularly by Rucker and by Jellison, the first proof of the transmission of plague by a bird comes from the demonstration of plague bacilli in sticktight fleas removed from burrowing owls captured in an epizootic area.<sup>86</sup> These fleas also infest Cooper's hawk and domestic fowl and add another complicating factor to the epidemiology of plague.

Creel,<sup>87</sup> like many others, still feels that plague is spreading eastward in the United States and that it could probably have been stamped out had proper measures been taken when the diagnosis was made in the "first" case. Meyer,<sup>88</sup> however, properly questions this concept and summarizes the known facts. There is every reason to believe that sylvatic plague has been endemic in widespread areas among wild rodents on this continent for an unknown period and can never be eradicated with the means available at present. Neither is there any reason to

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83. Francis, E., and Felton, L. D.: Antitularemic Serum, Pub. Health Rep. **57**:44-55 (Jan. 9) 1942.

84. Ey, L. F., and Daniels, R. E.: Tularemia in Dogs, J. A. M. A. **117**:2071-2072 (Dec. 13) 1941.

85. Ransmeier, J. C., and Schaub, I. G.: Direct Cultivation of Bacterium *Tularensis* from Human Blood Drawn During Life and at Autopsy: Report of Three Fatal Cases of Tularemia with Brief Notes on Two Others, Arch. Int. Med. **68**:747-762 (Oct.) 1941.

86. Wheeler, C. M.; Douglas, J. R., and Evans, F. C.: The Role of the Burrowing Owl and the Sticktight Flea in the Spread of Plague, Science **94**:560-561 (Dec. 12) 1941.

87. Creel, R. H.: Plague Situation in the Western United States, Am. J. Pub. Health **31**:1155-1162 (Nov.) 1941.

88. Meyer, K. F.: The Known and the Unknown in Plague, Am. J. Trop. Med. **22**:9-36 (Jan.) 1942.

believe that plague will ever cause the havoc it did in past centuries, unless the complete disintegration of civilization occurs. If measures to prevent it must eventually be undertaken at some time, the most feasible method is to establish a rodent-free zone around the community in question.

Meyer also points out that there is some encouragement for the use of antiplague serum in large doses therapeutically, but that vaccine, although it may reduce mortality, has never controlled an outbreak. The relative merits of the Haffkine type of vaccine or the live "attenuated" bacilli are still unsettled. Another report<sup>89</sup> was made of vaccination of more than 2,000,000 subjects with living virulent plague bacilli, without harmful consequences.

Two fatal cases of plague probably contracted from ground squirrels occurred in California.<sup>89a</sup>

Macchiavello<sup>90</sup> found that plague in Brazil increased with heavy rains and decreased with drought and a dispersion of rats from a community. High atmospheric temperature also obliges the vector flea, *Xenopsylla cheopis*, to remain in rat nests, thus keeping plague subterranean and away from human beings until the temperature falls. Numerous other epizootic diseases occur with plague in rodents. Sylvatic plague has not yet been reported in Brazil.

In the cases of plague in human beings the disease was generally milder than "classic" plague, with less bubonic suppuration and no pneumonia. Other forms in children were characterized by mild transitory symptoms. Macchiavello described 9 cases of a "new" clinical type of plague called multiglandular fever, characterized by septicemia; fever; wasting; anemia; multiple abscesses; a prolonged course, like that previously described by Meyer, and a low mortality. A case of combined infection with *Pasteurella pestis* and *Pasteurella pseudotuberculosis rodentium* was included in the series reported by Macchiavello.

Another case, the sixth, of infection with *Past. pseudotuberculosis rodentium* was reported<sup>91</sup> in the United States.

*Leprosy.*—After many previous unsuccessful or supposedly successful but unrecognized trials, attempts to transmit leprosy to experimental

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89. Otten, L.: A Live Plague Vaccine and the Results, Mededeel. v. d. dienst. d. volksgezondh. in Nederl.-Indië **30**:61, 1941.

89a. Plague Infection Reported in the United States During 1941, Pub. Health Rep. **57**:903-905 (June 12) 1942.

90. Macchiavello, A.: Some Special Epidemiological and Clinical Features of Plague in Northeastern Brazil, Pub. Health Rep. **56**:1657-1661 (Aug. 15) 1941.

91. Moss, E. S., and Battle, J. D.: Human Infection with *Pasteurella Pseudotuberculosis Rodentium* of Pfeiffer: Report of Case, Am. J. Clin. Path. **11**:677-699 (Sept.) 1941.

animals were revived by two investigators. Loving<sup>92</sup> caused chronic lesions in rabbits after inoculation with Duval's chromogenic acid-fast strain of *Bacillus leprae*. Nodules developed at the site of inoculation, and bacilli were present in the necrotic areas for as long as eight to nine months. Fite<sup>93</sup> inoculated 154 rats with emulsions of lepromatous nodules from human beings together with mucin or agar. Of these rats, a leprous process developed in 6 at the site of infection after eighteen months.

A fatal case of infection with *Bacillus violaceus* was reported.<sup>94</sup>

#### VIRUS DISEASES

*Colds and Influenza.*—Few persons realize the amount of time lost through mild infections of the respiratory tract. One study of the subject, conducted by the American Institute of Public Opinion,<sup>95</sup> shows an estimated total of 18,000,000 cases in one week in December.

Spiesman<sup>96</sup> gave massive doses of vitamin A and vitamin D separately to two groups of persons, but no effect either on the prevention or on the severity of colds was noted. When the two vitamins were combined, however, colds were significantly reduced, though it is hard to see why, and one wonders what method of control was used.

*Influenza.*—A new strain of influenza virus, different from virus A but closely related to virus B, was isolated during an epidemic in California.<sup>97</sup> Several other epidemic outbreaks were reported. Influenza A predominated in Boston in the winter of 1940-1941,<sup>98</sup> but in many cases there was no evidence of infection either with A or with B virus, suggesting that still other unidentified agents may be operative.

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92. Loving, W. L.: The Experimental Infection of Rabbits with Duval's Chromogenic Acid-Fast *Bacillus* from Human Leprosy, *J. Infect. Dis.* **68**:193-206 (May-June) 1941.

93. Fite, G. L.: Development of a Leprous Process in Rats at the Site of Inoculation with Material from Human Leprosy, *Pub. Health Rep.* **56**:1919-1922 (Sept. 26) 1941.

94. Schattenberg, H. J., and Harris, W. H.: A Definite and Unique Occurrence of Rapidly Fatal Infections Caused by *Bacillus Violaceus Manilae*, *J. A. M. A.* **117**:2069-2070 (Dec. 13) 1941.

95. Gallup Survey of Common Colds, *Medical News*, *J. A. M. A.* **118**:241 (Jan. 17) 1942.

96. Spiesman, I. G.: Massive Doses of Vitamins A and D in Prevention of Common Cold, *Arch. Otolaryng.* **34**:787-791 (Oct.) 1941.

97. Eaton, M. D., and Beck, M. D.: A New Strain of Influenza B Isolated During an Epidemic in California, *Proc. Soc. Exper. Biol. & Med.* **48**:177-180 (Oct.) 1941.

98. Pearson, H. E.; Eppinger, E. C.; Dingle, J. H., and Enders, J. F.: A Study of Influenza in Boston During the Winters 1940-41, *New England J. Med.* **225**:763-770 (Nov. 13) 1941.

Influenza preceded and apparently predisposed many patients to pneumococcic and staphylococcic pneumonia. Similar findings were reported by Lennette and his associates<sup>99</sup> in fifteen observed epidemics. Influenza A was causally related to more than 50 per cent of cases; influenza B, to only a few, and in 30 per cent of cases no virus was isolated. Epidemics apparently have diverse causes, and several types of virus are usually operative. The demonstration of one virus alone does not prove that the disease is of the same origin in all cases. Andrewes and associates<sup>100</sup> report influenza A virus as causing 79 per cent of infections in one epidemic in England. In a later study<sup>101</sup> evidence of the participation of influenza B was present. In more than half the cases in one epidemic the disease was caused by some agent other than influenza virus A or B.

An epidemic influenza-like disease in Minnesota in May 1939 could not be identified with influenza A.<sup>102</sup> Subsequent tests on nasopharyngeal washings kept frozen for nineteen months revealed the presence of influenza B. Serologic tests showed that the number of subclinical infections was equal to the number of persons actually sick. The clinical features of influenza A are so similar to those of influenza B as to be indistinguishable.

*Influenza Vaccine.*—Intensive studies were made to test the value of the vaccines already developed and to bring about an improvement in the technic in the hope of providing a more efficient method of prophylaxis. With methods in use at present the reported reduction of 50 per cent in the incidence of influenza A, as recorded by Horsfall's group,<sup>103</sup> is not great enough to control the disease. The specific antibodies evoked by vaccine were often of a titer equal to that encountered in normal persons, and protection against influenza was in direct proportion to the increase of demonstrable antibodies. Unfortunately, infection with the virus of influenza A was not prevented in all cases by vaccination with complex influenza A vaccine, and as would be expected, the incidence of influenza caused by virus B and influenza of unknown cause was not affected in the group studied.

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99. Lennette, E. H.; Rickard, E. R.; Hirst, G. K., and Horsfall, F. L.: *Diverse Etiology of Epidemic Influenza*, Pub. Health Rep. **56**:1777-1787 (Sept. 5) 1941.

100. Andrewes, C. H.; Glover, R. E.; Hudson, W. P.; Lush, D., and Stuart-Harris, C. H.: *Influenza in England in 1940-41*, Lancet **2**:387-388 (Oct. 4) 1941.

101. Lush, D.; Stuart-Harris, C. H., and Andrewes, C. H.: *The Occurrence of Influenza B in Southern England*, Brit. J. Exper. Path. **22**:302-304 (Dec.) 1941.

102. Nigg, C.; Eklund, C. M.; Wilson, D. E., and Crowley, J. H.: *Study of an Epidemic of Influenza B*, Am. J. Hyg. **35**:265-284 (March) 1942.

103. Horsfall, F. L.; Lennette, E. H.; Rickard, E. R., and Hirst, G. K.: *Studies on the Efficacy of a Complex Vaccine Against Influenza A*, Pub. Health Rep. **56**:1863-1875 (Sept. 19) 1941.

Experiments made in California<sup>104</sup> to test the relative value of Horsfall's complex distemper-influenza A virus vaccine and a living virus vaccine failed to show significant differences. In one test one vaccine gave slightly better results, and in the second, the other. The results of another group<sup>105</sup> of investigators were similar and led the authors to state that none of the many experiments with active and with inactive virus has resulted in conclusive proof of the effectiveness of vaccine against influenza A. Nevertheless, in these studies there was a reduction of incidence of the disease in a vaccinated group (13 to 15 per cent) as compared with controls (25 to 43 per cent), but influenza A developed subsequently in several vaccinated persons.

The results of a further study<sup>106</sup> at Letchworth Village, N. Y., are discouraging. Specific resistance in the interepidemic period could not be increased with vaccine. Influenza A occurred later not only among those persons recently vaccinated but in those vaccinated for four successive years. There was no significant difference in the incidence of acute disease of the respiratory tract among the inoculated persons and that in the controls. Nor was there a significant rise in the complement-fixing titer for influenza A after inoculation and subsequent infection. The incidence of influenza A was the same in persons with high or low titer. Clinical infection during one season also failed to protect against succeeding attacks.

Other studies<sup>107</sup> were made to test the nonspecific effect of the usual gamut of bacteria contained in commercially prepared so-called "cold" vaccines added to specific influenza vaccine, but no evidence of an adjuvant effect was noted.

According to Eaton and Martin,<sup>108</sup> the allantoic fluid vaccine for influenza B inactivated by formaldehyde was effective in evoking a rela-

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104. Martin, W. P., and Eaton, M. D.: Experiments on Immunization of Human Beings Against Influenza A, *Proc. Soc. Exper. Biol. & Med.* **47**:405-409 (June) 1941.

105. Brown, J. W.; Eaton, M. D.; Meiklejohn, G.; Lagen, J. B., and Kerr, W. J.: An Epidemic of Influenza: Results of Prophylactic Inoculation of a Complex Influenza A-Distemper Vaccine, *J. Clin. Investigation* **20**:663-669 (Nov.) 1941.

106. Siegel, M.; Muckenfuss, R. S.; Schaeffer, M.; Wilcox, H. L., and Leider, A. G.: A Study in Active Immunization Against Epidemic Influenza and Pneumococcus Pneumonia at Letchworth Village: IV. Results in an Epidemic of Influenza A in 1940-1941, *Am. J. Hyg.* **35**:186-230 (March) 1942.

107. Ungar, J., and Hunwicke, R. F.: The Value of the Non-Specific Factor in Experimental Immunization with Influenza Virus, *Brit. M. J.* **2**:12-13 (July 5) 1941.

108. Eaton, M. D., and Martin, W. P.: Immunization with Inactive Virus of Influenza B: Comparison of Antibody Response with That Produced by Infection, *Pub. Health Rep.* **57**:445-451 (March 27) 1942.

tively high antibody response in human subjects, but since the complement-fixing antibodies were weaker, the antigenic stimulus of vaccine was different from that of actual infection. The effectiveness of any vaccine is not necessarily dependent on the measurable antibody response.

Attempts were made to control influenza by the use of aerosols sprayed into the air.<sup>109</sup> Robertson and his associates<sup>110</sup> found the vapor of propylene glycol effective in preventing influenza in mice placed in an atmosphere laden with influenza virus in fine suspension.

Studies on the mode of spread of infection with influenza virus confirmed the important views of Wells that infection may be conveyed by means other than visible droplets expelled from the respiratory tract. Andrewes and Glover<sup>111</sup> placed normal ferrets and ferrets inoculated with influenza A virus in closed spaces, yet separated so as to prevent direct spraying with infected droplets. In spite of this barrier the exposed animals contracted the disease, presumably from microscopic particles of virus wafted through the air. When adequate ventilation was provided, with windows left open, no cross infection took place.

Glover<sup>112</sup> made similar experiments but with double infection by influenza virus and hemolytic streptococci, which were thought to play so important a role in the epidemic of 1918-1919. Normal ferrets easily contracted the dual infection when placed in cages with infected animals, but if they were separated from them by a barrier, only the influenza infection was transmitted, unless the recipient animals had previously been inoculated with influenza virus. Under the last-named circumstances the injurious action of influenza on the mucous membrane seemed to be specific in preparing the field for the invasion of streptococci, since irritation with chemicals failed to do so.

The amount of influenza virus suspended in air seemed to be important in direct proportion to the degree of severity of resultant infection in exposed animals.<sup>113</sup> A heavy suspension caused the death of all

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109. Henle, W., and Zellat, J.: Effect of Propylene Glycol Aerosol on Air-Borne Virus of Influenza A, *Proc. Soc. Exper. Biol. & Med.* **48**:544-547 (Nov.) 1941.

110. Robertson, O. H.; Loosli, C. G.; Puck, T. T.; Bigg, E., and Miller, B. F.: The Protection of Mice Against Infection with Air-Borne Influenza Virus by Means of Propylene Glycol Vapor, *Science* **94**:612-613 (Dec. 26) 1941.

111. Andrewes, C. H., and Glover, R. E.: Spread of Infection from the Respiratory Tract of the Ferret: I. Transmission of Influenza A Virus, *Brit. J. Exper. Path.* **22**:91-97 (April) 1941.

112. Glover, R. E.: Spread of Infection from the Respiratory Tract of the Ferret: II. Association of Influenza A Virus and Streptococcus Group C, *Brit. J. Exper. Path.* **22**:98-107 (April) 1941.

113. Wells, W. F., and Henle, W.: Experimental Air-Borne Disease: Quantitative Inoculation by Inhalation of Influenza Virus, *Proc. Soc. Exper. Biol. & Med.* **48**:298-301 (Oct.) 1941.

mice; a less heavy one caused pulmonary lesions only, and a dilute suspension failed to cause infection at all. When type I pneumococci were added to the spray simultaneously or five days later, the resulting pulmonary infections were more severe. The pulmonary lesions, however, looked the same as in those animals infected with virus alone.

The level of specific neutralizing antibodies in the blood of normal persons is said to be of value in determining their susceptibility to influenza A or B.<sup>114</sup> The relation is specific, since a high level of antibodies to one virus does not indicate resistance to the other or to influenza-like disease of undetermined origin. In one study<sup>115</sup> a sharp increase in virus-inactivating bodies developed in the nasal secretion in 9 of 10 patients with influenza A. The response was often parallel to the increase of similar antibodies in the blood and indicates that an important immune mechanism exists in nasal secretions.

Influenza virus was present in the feces of mice three days after intranasal inoculation.<sup>116</sup> It is probable, of course, that the virus was merely coughed up and swallowed, but the possibility of actual multiplication in the gastrointestinal tract was raised.

Interesting experiments<sup>117</sup> were made to determine the effects of various conditions which supposedly reduce resistance to infection with influenza. An unusual degree of heat, of cold and of fatigue failed to make test mice more susceptible to infection than control animals. This experience is in line with observations made on human beings in the epidemic of 1918-1919, when influenza occurred regardless of the physical condition of the victims. Severe deficiency either of vitamin A or of vitamin C likewise failed to have any effect on the level of demonstrable antibodies for influenza or on the phagocytic activity of leukocytes in human subjects.<sup>118</sup>

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114. Rickard, E. R.; Horsfall, P. L.; Hirst, G. K., and Lennette, E. H.: The Correlation Between Neutralizing Antibodies in Serum Against Influenza Viruses and Susceptibility to Influenza in Man, *Pub. Health Rep.* **56**:1819-1834 (Sept. 12) 1941.

115. Francis, T., and Brightman, I. J.: Virus-Inactivating Capacity of Nasal Secretions in the Acute and Convalescent Stages of Influenza, *Proc. Soc. Exper. Biol. & Med.* **48**:116-117 (Oct.) 1941.

116. Sarracino, J. B., and Soule, M. B.: Isolation of Virus from Fleas of Mice Receiving Intranasal Inoculations of Epidemic Influenza Virus, *Proc. Soc. Exper. Biol. & Med.* **48**:188-191 (Oct.) 1941.

117. Sarracino, J. B., and Soule, M. H.: Effect of Heat, Cold, Fatigue and Alcohol on Resistance of Mice to Human Influenza Virus, *Proc. Soc. Exper. Biol. & Med.* **48**:183-186 (Oct.) 1941.

118. Feller, A. E.; Roberts, L. B.; Ralli, E. P., and Francis, T.: Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, *J. Clin. Investigation* **21**:121-137 (March) 1942.



*"Virus" Pneumonia.*—Two minor outbreaks, both in schools, were reported<sup>119</sup> of the disease, called for convenience "virus" pneumonia. Adams and his associates<sup>120</sup> studied a second epidemic of a severe form of "primary virus pneumonitis" among young infants, with a mortality rate of 14 per cent. Cytoplasmic inclusion bodies were present in the epithelial cells in the lungs of the infants who died and in cells in smears of material from the throats of 85 per cent of the others. No virus was isolated.

In several attempts to discover the cause of this disease, or group of diseases, numerous agents have been isolated, as mentioned in last year's review.<sup>121</sup> More recent studies have provided further interesting data. The virus isolated last year by Eaton and his co-workers from patients with atypical pneumonia was found to be antigenically related to the viruses of both psittacosis and meningopneumonitis.<sup>122</sup> Similarities and relations to the virus of lymphogranuloma venereum were also detected.<sup>123</sup> All four viruses cause pneumonia and meningitis in inoculated animals, are characterized by the formation of elementary bodies and have antigenic components common to each other. Of interest also is the report of positive complement fixation reactions in the blood of patients convalescent from atypical pneumonia with antigen from the virus of lymphogranuloma venereum and of meningopneumonitis, and in 5 of 8 cases of "virus pneumonia" the result of the Frei test was positive. The numerous apparent similarities of these viruses and of the diseases they cause both in human beings and in animals seem too convincing to regard the relation as coincidental. It has even been suggested that the viruses of psittacosis, a psittacosis-like disease, meningopneumonitis and lymphogranuloma venereum may have arisen from an original strain in the animal kingdom and have become diversified or modified by the invasion of or adaptation to various hosts.<sup>122</sup> What relation these viruses may have to some or to most cases of the so-called "virus" pneumonia is a matter of further test. It is possible that mem-

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119. Gallagher, J. R.: Acute Pneumonitis: Report of an Epidemic, *Yale J. Biol. & Med.* **13**:769-781 (July) 1941. Daniels, W. B.: Bronchopneumonia of Unknown Etiology in a Girls' School, *Am. J. M. Sc.* **203**:263-276 (Feb.) 1942.

120. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, *J. Pediat.* **20**:405-420 (April) 1942.

121. Reimann, H. A.: Infectious Diseases: A Review of Significant Publications in 1940-1941, *Arch. Int. Med.* **68**:325-368 (Aug.) 1941.

122. Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationship of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, *J. Exper. Med.* **75**:21-33 (Jan.) 1942.

123. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, *Proc. Soc. Exper. Biol. & Med.* **48**:528-531 (Nov.) 1941.

bers of the psittacosis group of viruses do cause certain instances of the syndrome called "virus" pneumonia.

Meyer and associates<sup>124</sup> reported the isolation of a psittacosis-like virus from the lung of a patient who had been exposed to pigeons. A similar virus was recovered from some of the pigeons, and the complement fixation reaction for psittacosis was positive in 63 per cent of the birds. In another study<sup>125</sup> a case of pneumonia in a patient living on a chicken farm where an epidemic disease among poultry existed led to an epidemiologic survey. Many of the chickens were found to be spontaneously infected with the psittacosis-like virus, and serum from other members of the family, who were not sick, gave a positive complement fixation reaction for psittacosis. Meyer names this psittacosis-like virus disease "ornithosis," to distinguish it from true psittacosis. Evidence of its widespread distribution among birds and poultry he feels renders it likely that human beings are occasionally infected and disease develops which is erroneously called "virus" pneumonia. Although psittacosis virus and the related ones discussed in a previous paragraph pass through certain filters, they have other characteristics, such as microscopically visible particles, which place them in a class apart from true filtrable viruses, and the pneumonia they cause should not be named "virus" pneumonia.

For the isolation of ornithosis virus from human sputum intracranial injection into mice or pigeons may be essential, although it is probable that intranasal injection into mice would be successful.<sup>125a</sup> Intraperitoneal injection may give negative results.

Alicandri<sup>126</sup> reports a case of psittacosis in a man whose only known contact with possible sources was with pigeons. The data given do not tell the nature of the contact. The patient's serum gave a positive complement fixation reaction to psittacosis in a dilution of 1:256.

In my own experience this year with 8 cases of "virus" pneumonia, the complement fixation reaction for psittacosis was moderately positive in 3 and strongly positive in 1, although nothing in the case histories indicated contact or association with the known carriers of the psittacosis or the ornithosis virus. Inoculation of sputum into mice gave no evi-

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124. Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, *Proc. Soc. Exper. Biol. & Med.* **49**:609-615 (April) 1942.

125. Meyer, K. F., and Eddie, B.: Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of a Human Infection, *Proc. Soc. Exper. Biol. & Med.* **49**:522-525 (April) 1942.

125a. Pinkerton, H., and Moragues, V.: Comparative Study of Meningopneumonitis Virus, Psittacosis of Pigeon Origin and Psittacosis of Parrot Origin, *J. Exper. Med.* **75**:575-580 (June) 1941.

126. Alicandri, H.: Psittacosis, *J. A. M. A.* **118**:1214 (April 4) 1942.

dence of presence of psittacosis as it is usually described. The Frei test performed in a few cases gave negative results. The positive complement fixation reactions suggest that one of the viruses of the psittacine group may have caused the disease.

Smadel and his associates<sup>127</sup> report 2 unusual fatal cases of lymphocytic choriomeningitis, in which the diagnosis was obscure clinically and was made only after the isolation of the virus from the brain, the blood and the lungs at necropsy. In both cases the outstanding postmortem observation was a patchy bronchopneumonia characterized chiefly by a mononuclear cell infiltrate. Thus is added another entity to the syndrome called "virus" pneumonia. The blood of 1 of my patients with "virus" pneumonia was strongly protective against the virus of lymphocytic choriomeningitis.

It appears now that the term "virus" pneumonia is justified to name a syndrome composed of numerous etiologic entities. The pneumonias caused by viruses of influenza, chickenpox, lymphocytic choriomeningitis and perhaps the mungoose-infecting virus can be included in this group. The psittacine group of viruses may cause a similar clinical form of pneumonia but are not regarded as true filtrable viruses by some, and other agents not viruses, such as the *Rickettsia* of "Q" fever, the protozoan *Toxoplasma* and the fungus *Coccidioides immitis*, may give rise to atypical pneumonia which is in many respects similar to those caused by viruses.

It appears from my own studies and from those of other investigators that still other unidentified forms of atypical pneumonia exist, which can be classified only after the etiologic agents are discovered. In an official statement<sup>128</sup> the Surgeon General of the Army proposes the term primary atypical pneumonia, etiology unknown, to classify the syndrome of "virus" pneumonia encountered in the Army medical service. The recommendation is good, but this designation need not be used in cases in which the etiologic agent is determined.

*Chickenpox*.—Two cases of severe chickenpox in adults, 1 fatal, were reported.<sup>129</sup> Pneumonia occurred in both cases, and at necropsy in 1 there was encountered a mononuclear cell exudate with the formation of alveolar linings, both of which were at one time thought to be characteristic of virus infection of the lung, but other irritants are now known

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127. Smadel, J. E.; Green, R. H.; Paltauf, R. M., and Gonzales, T. A.: Lymphocytic Choriomeningitis: Two Human Fatalities Following an Unusual Febrile Illness, *Proc. Soc. Exper. Biol. & Med.* **49**:683-686 (April) 1942.

128. Primary Atypical Pneumonia, Etiology Unknown, Official Statement, *War Med.* **2**:330-333 (March) 1942.

129. Waring, J. J.; Neuburger, K., and Geever, E. F.: Severe Forms of Chickenpox in Adults, with Autopsy Observations in a Case with Associated Pneumonia and Encephalitis, *Arch. Int. Med.* **69**:384-408 (March) 1942.

to cause similar changes. Acute toxic encephalitis and nephrosis were also present.

*Poliomyelitis.*—A number of important contributions to the knowledge of poliomyelitis were made, some of them contradictory, but all will probably fit finally into the complex pattern.

Report of detailed studies by Howe and Bodian fills most of the August 1941 number of *The Bulletin of the Johns Hopkins Hospital*. In essence, their work indicates that there may be various portals of entry of the virus. In most of a series of fatal cases the olfactory bulbs were not invaded, suggesting that the virus entered elsewhere than the respiratory tract. The alimentary tract appears to be an important focus for the proliferation of the virus, and the spinal cord, the primary site of invasion of the central nervous system. In experimental studies cutting the spinal cord and sympathetic nerves did not hinder the spread of the virus to other parts of the nervous system, indicating a possible transit through the lymphatics, the blood or unusual pathways, such as the vagus nerve. The virus was estimated to travel along nerves at the rate of 2.4 mm. per hour. In other experiments clinical evidence of the disease appeared to be arrested at any stage after invasion of the nervous system. Since the spinal cord is not always involved, symptoms of encephalitis alone may occur without paralysis and give rise to diagnostic confusion, particularly with other specific forms of encephalitis (see p. 163).

Sabin and Ward<sup>130</sup> investigated the excretion of the virus in the early stages of poliomyelitis and tried to find its source. The virus was regularly present in the stools but was not found in the nasal or the oral secretion or in the urine. The virus, therefore, probably does not get into the stool simply because it has been swallowed. It is much more likely to have originated from the walls of the digestive tract. The virus apparently does not invade the nervous system by way of the nose or multiply in the nervous system, since it was present in pharyngeal and in intestinal tissue but not in the nasal mucosa or in the olfactory bulbs.

Other observers<sup>131</sup> recovered the virus at necropsy from the contents of the colon in 26 per cent of patients, from the stools in 20 per cent of living patients and from the stools in 5 per cent of healthy persons in contact with patients. Virus was present in the tonsil-adenoid tissue, the spinal cord and the colonic contents in 73 per cent of patients who

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130. Sabin, A. B., and Ward, R.: Natural History of Human Poliomyelitis: II. Elimination of Virus, *J. Exper. Med.* **74**:519-530 (Dec.) 1941.

131. Kessel, J. F.; Moore, F. J.; Stimpert, F. D., and Fisk, R. T.: Occurrence of Poliomyelitis Virus in Autopsies, Patients and Contacts, *J. Exper. Med.* **74**:601-610 (Dec.) 1941.

died. Repeated examinations of the stools of 5 patients failed to reveal the presence of the virus after a month.

McClure and Langmuir<sup>132</sup> made studies to determine how frequently the virus of poliomyelitis appears in the feces of persons in a community when cases of the disease occur. Specimens from 40 persons were tested, including ones from 5 persons with clinical evidence of poliomyelitis. Stools from 20 of 27 contacts contained the virus.

Interesting experiments were made in studying the nature of air-borne poliomyelitis in monkeys.<sup>133</sup> Typical poliomyelitis developed in 10 of 60 monkeys exposed to virus suspended in air. Of these, 4 had had olfactory "blockade" with zinc sulfate solution and 6 had not. Examination of the olfactory bulbs in those not treated showed histologic lesions in each, but they were at times so slight as to suggest secondary rather than primary lesions and may not indicate the entrance of virus at this point. Because the olfactory route was excluded in 2 significant instances, and because the oropharyngeal and gastrointestinal routes have been excluded by long experience, it is highly probable that the portal of entry in rhesus monkeys, at least, is in the mucosa of the lower respiratory tract at or below the epiglottis, and in cynomolgus monkeys, in the oropharynx. The experiments suggest that poliomyelitis in human beings may in some cases be air borne and the lungs the portal of entry. The known presence of virus in the nasopharynx providing a source for air contamination and previous evidence of apparent contact infection support the suggestion. Infection may occur both through the respiratory tract and through the gastrointestinal tract. A case of poliomyelitis developing in a laboratory worker was reported.<sup>134</sup>

Further evidence of the importance of infection through human contact is supplied by Piszczek and his associates<sup>135</sup> in Chicago and by Casey,<sup>136</sup> who studied an epidemic in a sparsely populated area of Alabama. The spread of the disease from neighborhood to neighborhood and from person to person seemed in Casey's study to be directly related to human travel. The effective reservoir of the virus appeared, as in other contagious diseases, to be a patient within three days before

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132. McClure, G. Y., and Langmuir, A. D.: Search for Carriers in an Outbreak of Acute Anterior Poliomyelitis in a Rural Community: The Incidence of Virus in Feces, *Am. J. Hyg.* **35**:385-391 (March) 1942.

133. Faber, H. K., and Silverberg, R. J.: Experimental Air-Borne Infection with Poliomyelitis Virus, *Science* **94**:566-568 (Dec. 12) 1941.

134. Sabin, A. B., and Ward, R.: Poliomyelitis in a Laboratory Worker Exposed to the Virus, *Science* **94**:113-114 (Aug. 1) 1941.

135. Piszczek, E. A.; Shaughnessy, H. J.; Zichis, J., and Levinson, S.: Anterior Poliomyelitis: Study of an Outbreak in West Suburban Cook County, Ill.; Preliminary Report, *J. A. M. A.* **117**:1962-1965 (Dec. 6) 1941.

136. Casey, A. E.: Observations in an Epidemic of Poliomyelitis, *Science* **95**:359-360 (April 3) 1942.

or three days after the onset of the first prodromal symptom. The actual mode of infection was not discovered.

Lumsden's study<sup>137</sup> in Mississippi led to opposite conclusions. Epidemiologic studies suggested that the disease was spread not by personal contact but by unknown factors. These factors may include rats, mice, domestic fowl, cattle and flies or other insects.

In the course of the study the author encountered many erroneous diagnoses. Colds, coryza, tonsillitis, rheumatic fever, diarrhea, malaria and other disorders were called poliomyelitis. A few physicians even depended on a cutaneous reaction to Rosenow serum for the diagnosis. The number of wrong diagnoses exceeded the number of unreported cases later added to the series.

Studies are also being continued on the possibility of fly-borne infection. In one of them poliomyelitis virus was isolated in 2 instances from flies trapped in an environment where the disease occurred.<sup>138</sup> Toomey and his associates,<sup>139</sup> after many failures, also report isolation of the virus from flies trapped near a sewer. They apparently do not consider flies as an important factor, because the virus could not be consistently recovered from them in epidemic years, the disease does not always occur in crowded communities infested with flies and the peaks of epidemics do not always coincide with periods of greatest fly population.

Sabin and Ward<sup>140</sup> defend their views against opposing comments of Professor C. T. Brues, who minimizes the role of human contact in the causation of poliomyelitis. These authors regard poliomyelitis as resembling typhoid fever, for example, in which the chief reservoir is in human excreta and both direct and insect spread may be possible. They again point out that the disease also occurs in winter when flies are not responsible. To these views may be added the possibility of droplet infection, as discussed previously.

As in Lumsden's experience last year,<sup>141</sup> a South American<sup>142</sup> observed cases of poliomyelitis in human beings intimately associated with an acute infectious paralytic disease in poultry. A possible relation between the two diseases is obviously suggested.

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137. Lumsden, L. L.: An Epidemiological Study of Poliomyelitis in Mississippi in 1941, *Pub. Health Rep.* **57**:729-753 (May 15) 1942.

138. Paul, J. R.; Trask, J. D.; Bishop, M. B., and Melnick, J. L.: The Detection of Poliomyelitis Virus in Flies, *Science* **94**:395-396 (Oct. 24) 1941.

139. Toomey, J. A.; Takacs, W. S., and Tischer, L. A.: Poliomyelitis Virus from Flies, *Proc. Soc. Exper. Biol. & Med.* **48**:637-639 (Dec.) 1941.

140. Sabin, A. B., and Ward, R.: Insects and Epidemiology of Poliomyelitis, *Science* **95**:300-301 (March 20) 1942.

141. Lumsden, L. L.: "Sporadic" Poliomyelitis, *Pub. Health Rep.* **56**:992-1007 (May 9) 1941.

142. Preioni, C.: Origin of Acute Anterior Poliomyelitis, *Rev. Assoc. méd. argent.* **55**:676 (Sept. 15-30) 1941.

The relation of tonsillectomy and poliomyelitis was the subject of a recent review<sup>143</sup> and of editorial comment.<sup>144</sup> The striking difference in the number of instances of the bulbar form, 27 per cent, in tonsillectomized children, as compared with 4.2 per cent in children with tonsils, is referred to. Nonparalytic poliomyelitis apparently occurs in either group just as often as the bulbar and the spinal form combined. The removal of tonsils seems, therefore, to be determinant between the bulbar and the spinal type of the disease. The nasopharyngeal mucosa seems to be particularly vulnerable to invasion, and tonsillectomy should not be performed when poliomyelitis is prevalent.

Rosenow<sup>145</sup> used the new electron microscope to bolster his theory concerning the relation of streptococci and their filtrable forms to the cause of poliomyelitis. The granules shown in his photomicrographs, however, and in the preparations viewed by others are not distinctive of material from patients with poliomyelitis and cannot be interpreted as being specifically related to the disease.

Treatment: In another editorial<sup>146</sup> the subject of massage is discussed in treatment of the disease. Massage is clearly indicated if all motor units in paralyzed muscles are to retain their maximal physiologic activity, since muscle fibers are dependent for normal stimulation on their local reflexes and immobilization arrests the flow of these proprioceptive impulses as effectively as it abolishes the flow of lymph.

Two papers<sup>147</sup> advocate the adoption of the Kenny treatment of poliomyelitis as the fundamental treatment of the disease which should be instituted as soon as the diagnosis is established.

In an attempt to reevaluate the action of human convalescent serum in the prevention of poliomyelitis Kramer<sup>148</sup> was able to cause significant protection even if mice were treated twenty-four hours after cerebral inoculation. This is the first definite experimental evidence of the protective value of serum. There was no evident therapeutic effect. In

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143. Aycock, W. L.: Tonsillectomy and Poliomyelitis, *Medicine* **21**:65-94 (Feb.) 1942.

144. Tonsillectomy and Poliomyelitis, editorial, *J. A. M. A.* **118**:980-981 (March 21) 1942.

145. Rosenow, E. C.: Microdiplococci in Filtrates of Natural and Experimental Poliomyelitic Virus Compared Under the Electron and Light Microscopes, *Proc. Staff Meet., Mayo Clin.* **17**:99-106 (Feb. 18) 1942.

146. Physiologic Anatomy of Poliomyelitis, editorial, *J. A. M. A.* **117**:1980-1981 (Dec. 6) 1941.

147. Pohl, J. F.: Kenny Treatment of Poliomyelitis, *J. A. M. A.* **118**:1428-1433 (April 25) 1942. Daly, M. M. I.; Greenbaum, J.; Reilly, E. T.; Weiss, A. M., and Stimson, P. M.: The Early Treatment of Poliomyelitis with an Evaluation of the Sister Kenny Treatment, *ibid.* **118**:1433-1443 (April 25) 1942.

148. Kramer, S. D.: Protection in White Mice with Human Convalescent Serum Against Infection with Poliomyelitis Virus (Armstrong Strain), *Proc. Soc. Exper. Biol. & Med.* **48**:287-293 (Oct.) 1941.

another study<sup>149</sup> there was no evidence as to the effect of vitamin D on the spread of poliomyelitis along peripheral nerves.

*Encephalitis.*—The subject was recently reviewed by Dingle.<sup>150</sup> According to Leake,<sup>151</sup> the greatest epidemic of encephalitis on record occurred in the summer of 1941 in the north central states and adjacent Canadian provinces. In North Dakota there were 1,080 cases, an incidence of 167 per hundred thousand persons, and in Nebraska the fatality rate was 16 per cent. In general, the symptomatology was like that of the St. Louis type of encephalitis. The virus of western equine encephalitis was the principal cause, as proved by the serum neutralization test. Since the great majority of infections occurred in men, particularly those working in wheat fields, some insect vector and a source other than human beings and horses are suggested. The virus was indeed isolated from a prairie chicken shot during the epidemic.<sup>152</sup> In Arizona<sup>153</sup> a smaller epidemic was apparently caused by the virus both of equine and of St. Louis encephalitis, in this case predominantly the virus of the latter. A similar dual epidemic was studied in the Yakima Valley, Wash., by Hammon and Howitt.<sup>154</sup>

Hammon, Carle and Izumi<sup>155</sup> present further evidence that the virus called the St. Louis type is as much "equine" as those called eastern and western equine strains but manifests neurotropic tendencies much less often. In inoculation experiments with the St. Louis strain the authors failed to cause clinical symptoms in horses but did produce inapparent, or subclinical, infection resulting in the presence of virus in the blood and a high titer of serum antibody.

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149. Sabin, A. B.; Ward, R.; Rapaport, S., and Guest, G. M.: Neuroinvasiveness of Poliomyelitis Virus in Relation to Vitamin D Nutrition, *Proc. Soc. Exper. Biol. & Med.* **48**:451-454 (Nov.) 1941.

150. Dingle, J. H.: The Encephalitides of Virus Etiology, *New England J. Med.* **225**:1014-1022 (Dec. 25) 1941.

151. Leake, J. P.: Epidemic of Infectious Encephalitis, *Pub. Health Rep.* **56**:1902-1905 (Sept. 26) 1941.

152. Cox, H. R.; Jellison, W. L., and Hughes, L. F.: Isolation of Western Equine Encephalitis Virus from Naturally Infected Prairie Chicken, *Pub. Health Rep.* **56**:1905-1906 (Sept. 26) 1941.

153. Meiklejohn, G., and Hammon, W. M.: Epidemic of Encephalitis, Predominantly of the St. Louis Type in Pinal County, Ariz., *J. A. M. A.* **118**:961-964 (March 21) 1942.

154. Hammon, W. M., and Howitt B. F.: Epidemiological Aspects of Encephalitis in the Yakima Valley, Washington: Mixed St. Louis and Western Equine Types, *Am. J. Hyg.* **35**:163-185 (March) 1942.

155. Hammon, W. M.; Carle, B. N., and Izumi, E. M.: Infection of Horses with St. Louis Encephalitis Virus, Experimental and Natural, *Proc. Soc. Exper. Biol. & Med.* **49**:335-340 (March) 1942.



In other studies <sup>156</sup> made in the Pacific Northwest, specific antibodies against both St. Louis encephalitis and western equine encephalitis were found in the blood of about 50 per cent of domestic fowl and in 20 per cent of quails, robins, sparrows, doves, hawks and other wild birds. Antibodies were also found in 51 per cent of horses, cows, sheep, pigs and other domestic animals except the cat. Tests were positive in only 8 per cent of rodents. Similar observations were made by Howitt and van Herick.<sup>157</sup> These investigators find it difficult to understand why fowl which possess antibodies are susceptible to infection with either virus. The demonstrable immune bodies, it appears, may not always signify previous infection. There is also no need to suppose that the St. Louis variety suddenly spread to the Pacific Coast. It is more likely that the disease is widely endemic and should not have received a limiting geographic name.

Parallel searches for evidence of infection in insects were made. Hammon and his co-workers <sup>158</sup> found the virus both of St. Louis and of Western equine encephalitis in the mosquito *Culex tarsalis* in the epidemic area. Ticks may be experimentally infected,<sup>159</sup> and Wheeler <sup>160</sup> in Kansas reports studies in which the virus of western equine encephalitis was found in 50 per cent of assassin bugs (*Microtonus purcis*), which feed on human beings and animals, possibly horses and rodents. He reports the case of a boy whose illness had after-effects typical of ones often occurring in cases of anterior poliomyelitis; the blood gave a strongly positive reaction for Western equine encephalitis. This occurrence indicates a type of mistake in diagnosis which is probably not uncommon.

In discussing the control of the three known American encephalitides, the St. Louis, the eastern equine and the western equine form, Hammon <sup>161</sup> suggests that the three be considered as closely related, since

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156. Hammon, W. M.; Gray, J. A.; Evans, F. C.; Izumi, E. M., and Lundy, H. W.: Western Equine and St. Louis Encephalitis Antibodies in the Sera of Mammals and Birds from an Endemic Area, *Science* **94**:305-307 (Sept. 26) 1941.

157. Howitt, B. F., and van Herick, W.: Neutralizing Antibodies Against St. Louis and Western Equine Encephalitic Viruses in Horses and Fowl, *Proc. Soc. Exper. Biol. & Med.* **48**:247-250 (Oct.) 1941.

158. Hammon, W. M.; Reeves, W. C.; Brookman, B.; Izumi, E. M., and Gjullin, C. M.: Isolation of the Viruses of Western Equine and St. Louis Encephalitis from *Culex Tarsalis* Mosquitoes, *Science* **94**:328-330 (Oct. 3) 1941.

159. Blattner, R. J., and Heys, F. M.: Experimental Transmission of St. Louis Encephalitis to White Swiss Mice by *Dermacentor Variabilis*, *Proc. Soc. Exper. Biol. & Med.* **48**:707-710 (Dec.) 1941.

160. Wheeler, J. A.: Western Equine Encephalitis Occurring Among Human Beings in Kansas During the Summer of 1941, *J. A. M. A.* **117**:1972-1973 (Dec. 6) 1941.

161. Hammon, W. M.: Suggestions for the Possible Control of the American Summer Encephalitides, *Correspondence, J. A. M. A.* **118**:66-68 (Jan. 3) 1942.

they affect similar hosts and mosquitoes. They are probably impossible to control because of the widespread endemicity, and as in the case of plague, it may be better to learn to live with them than to fight them ineffectively. However, mosquito control, specific vaccination of human beings and horses, zoning restrictions and extermination of wild life (obviously impossible) may all help to reduce the incidence of the disease in human beings.

One might gather from tabular classifications that the problem of diagnosing encephalitis in human beings etiologically is relatively simple and that in most cases the disease falls into one of several well defined entities. That such is not the case is indicated in the previous paragraph and in the reports from several laboratories that in at least 80 per cent of cases encephalitis cannot be diagnosed etiologically by the methods available at present. Further evidence of the existence of at least one still unclassified form was presented by Price at the May meeting of the American Society of Clinical Investigation. Four cases of meningo-encephalitis occurred almost simultaneously in a community. All tests applied to the blood and the spinal fluid failed to allow etiologic classification with the known forms.

*Lymphocytic Choriomeningitis.*—The subject was recently reviewed by Farmer and Janeway.<sup>162</sup> Milzer<sup>163</sup> transmitted lymphocytic choriomeningitis to guinea pigs by the mosquito *Aedes aegypti* but only at temperatures between 26 and 34 C. Transmission occurred from seven to thirty-eight days after the insect fed on an infected animal. The disease was also transmitted by bedbugs at temperatures between 22 and 25 C. Bedbugs are unable to transmit infection by biting alone. The virus is contained in the feces, which when rubbed into abrasions may cause infection. Mice and guinea pigs were also infected by swallowing infected mites. The virus persists through one or two larval stages.

Smadel and his associates<sup>127</sup> report 2 unusual fatal cases of lymphocytic choriomeningitis, with necropsy observations, as referred to on page 158.

*Yellow Fever.*—By the use of the mouse protection test, studies<sup>164</sup> in Africa show that yellow fever is spread much more widely than heretofore believed. Instead of being confined to the west coast alone, evidence of infection extends as far east as the Nile valley. The problem seems about as complex and extensive as in South America, where jungle yellow fever occurs throughout an enormous area. The problem

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162. Farmer, T. W., and Janeway, C. A.: Infection with the Virus of Lymphocytic Choriomeningitis, *Medicine* **21**:1-64 (Feb.) 1942.

163. Milzer, A.: Studies on the Transmission of Lymphocytic Choriomeningitis Virus by Arthropods, *J. Infect. Dis.* **70**:152-172 (March-April) 1942.

164. Findlay, G. M.; Kirk, R., and MacCallum, F. O.: Yellow Fever and the Anglo-Egyptian Sudan: Distribution of Immune Bodies to Yellow Fever, *Am. J. Trop. Med.* **35**:121 (Dec. 31) 1941.

of transmission and of insect vectors in South America has recently been solved<sup>165</sup> by the discovery that a newly incriminated mosquito (*Haemogamus*) resides not necessarily near the surface of water and low lying ground but in tree tops. These mosquitoes unfortunately survive throughout the dry season and carry the causative virus over from one rainy season to the next and thus serve as a permanent reservoir. Jungle yellow fever frequently occurs in men engaged in felling trees.

Jaundice has occurred in a high percentage of soldiers several weeks to several months after vaccination against yellow fever. Whether the disease is a mild form of yellow fever has not been determined.

#### OTHER SPECIFIC INFECTIOUS DISEASES

*Rickettsial Disease.*—For years it was believed that the mortality rate from Rocky Mountain spotted fever was much greater in certain areas of the West than elsewhere in this country. Evidence now indicates this to be more apparent than real. In an epidemiologic study<sup>166</sup> the disease as it occurs in the eastern states was found to affect chiefly children, who are more exposed to ticks through recreational activities, and in the West men, whose occupations often favor exposure, are more often victims. Since the mortality rate from the disease is lower in children, the apparent difference in mortality rate is partly explained. When the fatality rates are corrected for age difference, they are about the same in both areas.

Further reasons may be found in the fact<sup>167</sup> that highly virulent strains of *Rickettsia* have been encountered in the East, and a strain of low virulence was found in the West, so that the terms eastern and western are no longer applicable. Designation at present is best made on the basis of virulence for guinea pigs.

Rocky Mountain spotted fever and typhus, usually thought to be caused by completely different or unrelated rickettsias, are, according to recent studies, not so different after all. Castaneda and Silva<sup>168</sup> demonstrated reciprocal cross immunity reactions between the rickettsias of both diseases, as I did in 1935 in studying a strain isolated in Minnesota which seemed to have characteristics of both varieties. This trend of thought is in line with evidence favoring a variety of similar strains among groups of infectious agents, such as the psittacine group of viruses and the influenza viruses.

165. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1941, New York, 1942, p. 13.

166. Topping, N. H.: Rocky Mountain Spotted Fever: A Note on Some Aspects of Its Epidemiology, Pub. Health Rep. **56**:1699-1703 (Aug. 22) 1941.

167. Topping, N. H.: A Strain of Rocky Mountain Spotted Fever Virus of Low Virulence Isolated in the Western United States, Pub. Health Rep. **56**:2041-2043 (Oct. 17) 1941.

168. Castaneda, M. R., and Silva, R.: Immunologic Relationship Between Spotted Fever and Exanthematic Typhus, J. Immunol. **42**:1-14 (Sept.) 1941.

It is still uncertain as to whether typhus in mice can be transformed into the historic epidemic variety by rat-man-lice-man passage. In China Liu and Zia<sup>169</sup> present evidence that the strain in mice may be transmitted from man to man by body lice and give rise to epidemics. The problem of typhus fever in China is summarized in a paper by Liu, Zia, Chung and Wang.<sup>170</sup> Brigham<sup>171</sup> isolated two strains of endemic typhus from chicken fleas removed from rats.

A suitable animal for the study of typhus fever was found in the cotton rat.<sup>172</sup> Complement fixation tests developed in two laboratories<sup>173</sup> proved useful in determining both recent and past rickettsial infection.

Ominous warnings as to the danger of new typhus epidemics in the war-ravaged areas of eastern Europe appear. The number of cases in Poland, Hungary and Bulgaria, for example, have doubled or trebled between 1940 and 1941.<sup>174</sup> With continued disorganization of millions of people and increasing hardship and starvation, the outlook for a large outbreak is grim indeed. To combat this pestilence large scale studies are being undertaken to test the prophylactic value of the new antityphus vaccine developed by Cox. Controlled experimental studies<sup>175</sup> were made by members of the National Institute of Health in a large group of South American Indians in an area where epidemic typhus is endemic. The report of results of this trial is anxiously awaited. In laboratories persons working with typhus material contracted the disease in spite of vaccination.

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169. Liu, W. T., and Zia, S. H.: Studies on Murine Origin of Typhus Epidemics in North China: I. Murine Typhus Rickettsia Isolated from Body Lice in Garments of Sporadic Case, *Am. J. Trop. Med.* **21**:507-524 (July) 1941.

170. Liu, W. T.; Zia, S. H.; Chung, H. L., and Wang, C. W.: Typhus Fever in Peiping, Epidemiologic Considerations, *Am. J. Hyg.* **35**:231-250 (March) 1942.

171. Brigham, G. D.: Two Strains of Endemic Typhus Fever Virus Isolated from Naturally Infected Chicken Fleas (*Echidnophaga Gallinacea*), *Pub. Health Rep.* **56**:1803-1804 (Sept. 5) 1941.

172. Snyder, J. C., and Anderson, C. R.: The Susceptibility of the Eastern Cotton Rat, *Sigmodon Hispidus Hispidus* to European Typhus, *Science* **95**:23 (Jan. 2) 1942.

173. Bengston, I. A.: The Specificity of the Complement Fixation Test in Endemic Typhus Using a Rickettsial Antigen, *Pub. Health Rep.* **56**:1723-1727 (Aug. 29) 1941. Plotz, H., and Wertman, K.: The Use of the Complement Fixation Test in Rocky Mountain Spotted Fever, *Science* **95**:441-442 (April 24) 1942.

174. Danger of a Typhus Epidemic in Europe. *Statist. Bull. Metrop. Life Insur. Co.* **22**:7-9 (Nov.) 1941.

175. New Typhus Vaccine Being Tested in Bolivia, *Science* **94**:340 (Oct. 10) 1941.

Further studies<sup>176</sup> are reported on the value of typhus antiserum prepared in rabbits with typhus rickettsias grown in yolk membranes from chick embryos. Administration to guinea pigs as late as five days after inoculation with typhus has a beneficial therapeutic effect.

*Weil's Disease.*—Thus far at least 20 definite cases and 20 presumptive cases of leptospirosis, or Weil's disease, have been reported in American literature. Larson<sup>177</sup> adds 51 more. Even these represent only a small portion of the actual number of cases. The diagnosis is often not made or not reported, especially in the mild forms and in those without jaundice. Forty per cent of the series of 51 cases occurred from June to August. Stiles and Sawyer<sup>178</sup> summarize recent knowledge of the infection and regard it as an occupational hazard.

Packchanian<sup>179</sup> calls attention to the value of the agglutination test in making diagnoses in cases of suspected leptospirosis, but for absolute diagnosis it is essential to isolate *Leptospira icterohaemorrhagiae* from the patient's blood or urine. This, of course, can only be accomplished early in the disease because *Leptospira* disappears from the blood after about five days and from the urine in a month. An interesting point in his study is the demonstration of strongly positive agglutination reactions on the serum of 20 jaundiced dogs from widely separated places in the United States.

According to Morton,<sup>180</sup> the Syrian hamster is a convenient and satisfactory animal to use for the diagnosis of leptospirosis. Other investigators have also shown the value of this animal for the diagnosis of influenza, St. Louis encephalitis, lymphocytic choriomeningitis, meningopneumonitis and lymphogranuloma venereum.

*Rat Bite Fever.*—Larson<sup>181</sup> reports 3 cases of rat bite fever, in 1 of which the disease was probably caused by *Spirillum minus* and in the others by *Streptobacillus moniliformis*, the same bacterium which causes Haverhill fever. Rat bite fever caused by both agents has also been

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176. Wyckoff, R. W. G., and Bohnel, E.: Therapeutic Effect in Guinea Pigs of Hyperimmune Epidemic Typhus Antiserum, *Proc. Soc. Exper. Biol. & Med.* **49**:712-715 (April) 1942.

177. Larson, C. L.: Weil's Disease: A Report of Fifty-One Cases Occurring in Puerto Rico and the United States, *Pub. Health Rep.* **56**:1650-1656 (Aug. 15) 1941.

178. Stiles, W. W., and Sawyer, W. A.: Leptospiral Infection (Weil's Disease) as an Occupational Hazard, *J. A. M. A.* **118**:34-38 (Jan. 3) 1942.

179. Packchanian, A.: Positive Agglutination Tests in Suspected Cases of Weil's Disease, *Pub. Health Rep.* **56**:2145-2156 (Nov. 7) 1941.

180. Morton, H. E.: Susceptibility of Syrian Hamsters to Leptospirosis, *Proc. Soc. Exper. Biol. & Med.* **49**:566-568 (April) 1942.

181. Larson, C. L.: Rat-Bite Fever in Washington, D. C., Due to *Spirillum Minus* and *Streptobacillus Moniliformis*, *Pub. Health Rep.* **56**:1961-1968 (Oct. 3) 1941.

noted in Illinois,<sup>182</sup> and that caused by *S. moniliformis* alone, in Virginia.<sup>183</sup> Apparently rat bite fever is composed of at least two etiologic entities. The subject is reviewed by Brown and Nunemaker,<sup>184</sup> who present convincing evidence that both agents may cause disease and that the *S. moniliformis* infection is the more common. Contrary to Klieneberger's view, there was consistent reversion between the micro-organisms causing pleuropneumonia and *S. moniliformis*. Klieneberger regarded them as different micro-organisms living in symbiosis, but it is most likely that bacterial dissociation accounts for the transformation of one form into the other.

Bacteria of the pleuropneumonia group were once regarded as a possible cause of rheumatic fever or rheumatoid arthritis because of the arthritis they cause in animals. According to Preston,<sup>185</sup> the arthritis in animals is of the suppurative type and bears little resemblance to the disease in human beings.

Cases of relapsing fever and instances of ticks carrying the infection were reported from Oregon<sup>186</sup> and from Utah. The infection exists in most of the western states.

Welt<sup>187</sup> found that trichinosis could be induced in monkeys by feeding them one *Trichina* larva per gram of body weight. Fever, edema and eosinophilia developed. Antibodies, as demonstrated by the precipitin test, developed in the serum and in the urine after several weeks. The cutaneous test also may be valuable in diagnosis.

Pork infected with *Trichina* can be made safe for human consumption by proper freezing.<sup>188</sup> For example, the parasites may be killed by refrigeration of sections of pork not more than 6 inches (15 cm.) thick at 5 F. for twenty days. Lower temperatures require shorter exposure.

*Malaria*.—A causal relation between ferriheme, the pigment liberated by sporulating parasites of malaria, and the paroxysm of the

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182. Kirkwood, T., and Stoll, C. G.: Rat-Bite and Haverhill Fevers, Illinois M. J. **80**:141-144 (Aug.) 1941.

183. Hart, A. D.: Haverhill Fever Following Rat Bite, Virginia M. Monthly **68**:582-584 (Oct.) 1941.

184. Brown, T. M., and Nunemaker, J. C.: Rat-Bite Fever: A Review of the American Cases with Reevaluation of Etiology; Report of Cases, Bull. Johns Hopkins Hosp. **70**:201-328 (March) 1942.

185. Preston, W. S.: Arthritis in Rats Caused by Pleuropneumonia-Like Micro-Organisms and the Relationship of Similar Organisms to Human Rheumatism, J. Infect. Dis. **70**:180-184 (March-April) 1942.

186. Davis, G. E.: *Ornithodoros Hermsi* and Relapsing Fever in Oregon, Pub. Health Rep. **56**:2010-2012 (Oct. 10) 1941; *Ornithodoros Parkeri* and Relapsing Fever Spirochetes in Utah, *ibid.* **56**:2464-2468 (Dec. 26) 1941.

187. Welt, L. G.: Urinary Excretion of *Trichina* Antigen in Experimental Trichinosis, Proc. Soc. Exper. Biol. & Med. **48**:587-589 (Dec.) 1941.

188. Items, Science (supp.) **95**:14 (March 20) 1942.

disease has been suggested,<sup>189</sup> because of a similar reaction produced by the injection of ferrihemate solution in animals. It was shown, however, that the pigment is not liberated in soluble form from the plasmodia and is therefore not the cause of the paroxysm.

By using *Plasmodium knowlesi* antigen-coated collodion particles, according to Goodner's method, or by addition of collodion particles at the time of combining antigen and antibody, specific precipitin reactions in malaria in human beings were demonstrated by microscopic agglutination.<sup>190</sup> The test may prove to be of value in diagnosis.

*Fungous and Yeast Infections.*—An interesting group of cases of sporotrichosis among florists was described.<sup>191</sup> All patients had handled sphagnum moss and the flat fern, and all had had previous wounds of the skin. In a paper<sup>192</sup> entitled "Torula Infection of the Lungs and Central Nervous System," the lungs were scarcely mentioned in the 6 case reports. The description dealt chiefly with involvement of the central nervous system.

In a paper<sup>193</sup> describing an unusual case of endocarditis caused by a fungus, *Candida parakrusei*, in a habitual user of diacetylmorphine (heroin) the authors refer to 5 other cases of endocarditis of similar origin, all occurring in drug addicts. They feel that fungi isolated in cases of mycotic infection are often considered to be contaminants and are discarded as such, when actually they are the cause. In the case described the diacetylmorphine used was not found to contain spores of the fungus, but other samples may have been contaminated and may have accounted for the infection of the other addicts within the past two years. Another possible source of infection, of course, is the skin.

A case of histoplasmosis was reported from Brazil,<sup>194</sup> 1 from Michigan<sup>195</sup> and another from Illinois.<sup>196</sup> In the last-named case a

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189. Morrison, D. B., and Anderson, W. A. D.: On the Role of Parasite Pigment in the Malaria Paroxysm, *Pub. Health Rep.* **57**:161-174 (Jan. 30) 1942.

190. Dulaney, A. D., and House, V.: Precipitative Tests in Malaria, *Proc. Soc. Exper. Biol. & Med.* **48**:620-623 (Dec.) 1941.

191. Gastineau, F. M.; Spolyar, S. W., and Haynes, E.: Sporotrichosis: Report of Six Cases Among Florists, *J. A. M. A.* **117**:1074-1077 (Sept. 27) 1941.

192. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of Six Cases with Three Autopsies, *Arch. Int. Med.* **68**:57-79 (July) 1941.

193. Wikler, A.; Williams, E. G.; Douglass, E. D.; Emmons, C. W., and Dunn, R. C.: Mycotic Endocarditis: Report of a Case, *J. A. M. A.* **119**:333-336 (May 23) 1942.

194. Villela, E., and Madureira Para: Histoplasmosis in Child, *Rev. brasil. de biol.* **1**:449 (Dec.) 1941.

195. Ramsey, T. L., and Applebaum, A. A.: Histoplasmosis "Darling," *Am. J. Clin. Path.* **12**:85-94 (Feb.) 1942.

196. Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, *J. A. M. A.* **117**:436-437 (Aug. 9) 1941.

cutaneous test made with a filtrate of a culture of the causative fungus gave a specific reaction. Such a test may possibly serve as a helpful diagnostic aid. Histoplasmosis as a cause of ulcerative disease of the colon<sup>197</sup> is discussed on page 172.

Editorial comment<sup>198</sup> on histoplasmosis briefly summarizes the subject and states that thus far the disease has been invariably fatal. One wonders whether this is actually so or, whether the diagnosis is not made in cases of mild forms with recovery, as was once the case with coccidioidomycosis, as discussed in the next paragraph.

*Coccidioidomycosis.*—Only a few years ago coccidioidomycosis was diagnosed only in its most severe form as coccidioidal granuloma and was regarded as a disease of high mortality. Since the recognition of the mild forms of the infection, the concept of the disease has changed. It is actually a common disease in some localities, manifesting itself in most instances as a subclinical or an inapparent infection or as a minor infection of the respiratory tract, most often mistaken for the common cold or for influenza. In rare instances the chronic form may be characterized by persistent suppurative arthritis, with *Coccidioides immitis* easily demonstrable in the pus.<sup>199</sup> The severe, often fatal, forms with multiple granulomatous lesions or erythema nodosum are fortunately rare. In Smith's<sup>200</sup> experience coccidioidomycosis in endemic centers like the San Joaquin Valley in California is almost always mild and is mistaken for influenza, pneumonia, poliomyelitis or typhoid fever. It is thought that eventually most inhabitants of the region contract the infection. According to Winn,<sup>201</sup> 76 to 84 per cent of patients show a positive cutaneous reaction to injected coccidioidin. Similar views are expressed by Davis, Smith and Smith,<sup>202</sup> who report a small outbreak affecting 7 to 14 members of a party on a field trip who were probably infected by inhaling spore-laden dust. The victims became sick nine to fourteen days later.

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197. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: *Histoplasma Capsulatum* as a Cause of Chronic Ulcerative Enteritis, *J. A. M. A.* **118**:885-889 (March 14) 1942.

198. Histoplasmosis, editorial, *J. A. M. A.* **119**:265-266 (May 16) 1942.

199. Rosenberg, E. F.; Dockerty, M. B., and Meyerding, H. W.: Coccidioidal Arthritis: Report of a Case in Which Ankles Were Involved and Condition Was Unaffected by Sulfanilamide and Roentgentherapy, *Arch. Int. Med.* **69**:238-250 (Feb.) 1942.

200. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), *Am. J. Pub. Health* **30**:600-618 (June) 1940.

201. Winn, W. A.: Pulmonary Cavitation Associated with Coccidioidal Infection, *Arch. Int. Med.* **68**:1179-1214 (Dec.) 1941.

202. Davis, B. L.; Smith, R. T., and Smith, C. E.: An Epidemic of Coccidioidal Infection (Coccidioidomycosis), *J. A. M. A.* **118**:1182-1186 (April 4) 1942.



Roentgenographic studies<sup>203</sup> on these patients showed numerous diffuse patchy areas of infiltration which may be mistaken for "virus" pneumonia. Loeffler's pneumonia might be thought of because of the eosinophilia. Cavitation, which occurred in many involved areas, may seriously confuse the diagnosis with pulmonary tuberculosis unless etiologic studies are made. Diagnosis is made by the history of the illness, the location where the disease was contracted, the presence of double contoured spherules in the sputum, a positive reaction to coccidioidin, animal inoculation, agglutination and precipitin tests, leukocytosis with eosinophilia and patchy areas of density in the lungs with cavitation. In cases of the severe form chronic granulomatous lesions of the skin and erythema nodosum occur.

Shelton<sup>204</sup> tested nearly 900 soldiers in a camp in California with coccidioidin and found 14 to have acquired specific hypersensitivity during a three month period. Several cases of clinical coccidioidomycosis occurred in this camp, which is located in an area not previously known as an endemic focus.

In studies<sup>205</sup> made elsewhere to determine the source of infection, the fungus *Coccidioides* was cultivated directly from desert soil. Small rodents apparently may harbor the fungus and in turn contaminate the soil; the spores then become suspended in dust and air and are inhaled by man. In another study in Arizona, 25 of 105 small wild rodents harbored fungi, of which three were species of *Coccidioides*.

#### MISCELLANEOUS DISEASES

Several studies on the etiology of chronic ulcerative colitis were published. Acute and chronic enteritis, including ulceration of the mucosa of the colon, was produced in dogs by obstructing the lymphatic drainage of the ileocecal segment of intestine.<sup>206</sup> The presence of mesenteric lymphatic obstruction is sufficient to produce ulceration of the rectal mucosa without the agency of bacteria. These studies support the view that the disease may be initiated by noninfectious factors. Others<sup>207</sup> summarized the evidence implicating *Bacterium necrophorum* as the cause. It seems that this bacterium may predominate over others in the colon in some cases; it has been found in most cases and specific

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203. Powers, R. A., and Starks, D. J.: Acute (Primary) Coccidiomycosis: Roentgen Findings in a Group Epidemic, *Radiology* **37**:448-453 (Oct.) 1941.

204. Shelton, R. M.: A Survey of Coccidioidomycosis at Camp Robert, California, *J. A. M. A.* **118**:1186-1190 (April 4) 1942.

205. Emmons, C. W.: Isolation of *Coccidioides* from Soil and Rodents, *Pub. Health Rep.* **57**:109-111 (Jan. 23) 1942.

206. Poppe, J. K.: Reproduction of Ulcerative Colitis in Dogs, *Arch. Surg.* **43**: 551-558 (Oct.) 1941.

207. Dragstedt, L. R.; Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis: Summary of Evidence Implicating *Bacterium Necrophorum* as Etiologic Agent, *Ann. Surg.* **114**:653-662 (Oct.) 1941.

antibodies against it appear in the blood: The evidence presented thus far as to its etiologic relation to the disease is not particularly convincing. It is still uncertain whether this micro-organism, like Vincent's spirillum, is merely a saprophyte which thrives in tissue made necrotic by other causes.

Of interest is the report <sup>197</sup> of a case in which *Histoplasma capsulatum* was found in intestinal ulcers, the mesenteric lymph nodes and elsewhere and was apparently the cause of prolonged diarrhea. In a review of 25 previously reported cases of histoplasmosis the authors stated that similar lesions occurred in the intestine in 8 cases but in only 2 was there prolonged diarrhea. It would appear, as many investigators have already suggested, that chronic ulcerative colitis is a syndrome resulting from a variety of causes both infectious and noninfectious.

A peculiar "new" form of epidemic infectious conjunctivitis caused a perplexing problem in Hawaii in the summer of 1941.<sup>208</sup> The infection apparently entered California in the autumn. The cause has not been determined but is believed to be a filtrable virus. Infection seems to take place by contact, and after an incubation period of two to five days severe conjunctivitis occurs. The disease is self limiting and lasts from two to three weeks. No specific form of treatment is known.

Nettleship <sup>209</sup> inoculated the chorioallantoic membrane of chick embryos with filtered nasal washings from 8 patients with infectious mononucleosis and obtained positive results in 4 instances in the form of ectodermal proliferation and heavy monocytic cell infiltration. The reaction could be continued through four to fourteen passages but eventually disappeared. Attempts at animal transmission were unsuccessful.

Newman <sup>210</sup> had the unusual opportunity of studying an outbreak of infectious, or catarrhal, jaundice in a community. As the only physician in charge, he was able to observe all illnesses continuously and thus to correlate typical with atypical cases. The epidemic appeared at intervals in small series of cases and extended from January to April, involving 33 patients. Person to person contact seemed essential, and its spread by droplet infection seemed probable. Of importance was the occurrence of many cases of a mild form of apparently the same disease, but without jaundice, which no doubt would not have been associated with the epidemic had not a single physician observed all cases. In these atypical cases the condition could have been mistaken for meningitis, grip or appendicitis had they occurred as isolated instances.

208. Holmes, W. J.: Epidemic Infectious Conjunctivitis, *Hawaii M. J.* **1**:11-12 (Nov.) 1941.

209. Nettleship, A.: On Infectious Mononucleosis, *Proc. Soc. Exper. Biol. & Med.* **49**:116-117 (Feb.) 1942.

210. Newman, J. L.: Infective Hepatitis: The History of an Outbreak in the Lavant Valley, *Brit. M. J.* **1**:61-65 (Jan. 17) 1942.

A phytopathogenic bacterium discovered recently <sup>211</sup> as the cause of bacterial leaf spot of tobacco is highly virulent for rabbits, guinea pigs and mice, causing septicemia and death. Its ability to multiply in animals and plants is remarkable and is interesting from an evolutionary point of view. It is perhaps the first micro-organism discovered which is pathogenic both for plants and for animals.

#### DISINFECTION OF AIR

Wells, Wells and Wilder <sup>212</sup> report further study of the effects of radiant disinfection of air as a method to prevent the spread of contagious disease. The results were gratifying in that no contagious disease occurred among children in irradiated groups in two schools, while measles and mumps occurred among the controls. The primary object was not to postpone contagious diseases to later childhood, though this may at times be desirable, but to test the hypothesis that contagion may be controlled by irradiation, as in army barracks and among groups in which immediate protection against disease may be imperative.

Buchbinder <sup>213</sup> reviews modern work showing how important air-borne infection is and that the old "contact" theory of spread of infection is not adequate. He points out the germicidal effectiveness of sunlight and even of diffuse daylight.

The importance of stirring up dust and the resuspension of bacteria in air as an important source of infection are emphasized, especially when hemolytic streptococci are involved. One may point out how little attention has been paid to air-borne infection in operating room technic, yet it is surprising how few infections occur even during operations performed in an open room with 100 or more students scuffling about and raising dust. It has always seemed to me that "sterile technic" in operating rooms is greatly exaggerated and that thousands of dollars might be saved if unnecessary procedures were eliminated by some one with courage to show the way. Much may be learned in this respect from surgery in wartime conditions.

The author discusses chemical sprays as air disinfectants, such as hexylresorcinol, a solution of resorcinol in glycerin, organic smokes, sodium hypochlorite solution, propylene glycol, ethylene glycol and trimethylene glycol. He states that Twort has listed the first four in decreasing order of effectiveness. The possible injurious effect of aerosols on experimental subjects exposed to them over long periods is as yet unknown.

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211. Elrod, R. P., and Braun, A. C.: A Phytopathogenic Bacterium Fatal to Laboratory Animals, *Science* **94**:520-521 (Nov. 28) 1941.

212. Wells, W. F.; Wells, M. W., and Wilder, T. S.: The Environmental Control of Epidemic Contagion: An Epidemiologic Study of Radiant Disinfection of Air in Day Schools, *Am. J. Hyg.* **35**:97-121 (Jan.) 1942.

213. Buchbinder, L.: The Transmission of Certain Infections of Respiratory Origin: A Critical Review, *J. A. M. A.* **118**:718-730 (Feb. 28) 1942.

As little as 1 Gm. of propylene glycol in 2,000,000 to 4,000,000 cc. of air is bactericidal for pneumococci, streptococci, staphylococci, *H. influenzae* and other bacteria.<sup>213a</sup>

In another <sup>214</sup> practical application of prophylaxis against air-borne infection, air conditioning alone failed to prevent acute cross infections of the respiratory tract in infants, but air conditioning together with germicidal light barriers or with mechanical barriers was effective. Numerous other reports of favorable results of the use of germicidal light are referred to in this paper.

#### ANTIBIOTIC AGENTS

The subject of antibiotic agents has been reviewed by Waksman.<sup>215</sup> Since then other papers have appeared.

According to Rammelkamp,<sup>216</sup> different strains of staphylococci vary in their susceptibility to the action of tyrothricin, which together with the irregular development of resistance to the substance probably accounts for the different results obtained in treating patients with staphylococcic infections with this substance. Staphylococci grown in vitro are able to establish increasing resistances to the inhibitory and bacterial action of tyrothricin. Tyrothricin has no effect on *Lactobacillus acidophilus* in the intestines of mice when given orally.<sup>217</sup> Besides bacteriostatic and bactericidal activity, both tyrothricin and actinomycin A, a substance isolated from *Actinomyces antibioticus*, inhibit fibrinolysis by hemolytic streptococci and interfere with the coagulation of plasma by staphylococci.<sup>218</sup>

Bacteriologic culture medium containing tyrothricin is claimed to be helpful in isolating *Haemophilus influenzae* by inhibiting the growth of other bacteria.<sup>219</sup>

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213a. Robertson, O. H.; Bigg, E.; Puck, T. T., and Miller, B. F.: Bactericidal Action of Propylene Glycol Vapor on Microorganisms Suspended in Air, *J. Exper. Med.* **75**:543-609 (June) 1942.

214. Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Control of Cross Infections of the Respiratory Tract in a Nursery for Young Infants: A Preliminary Report, *J. A. M. A.* **118**:1271-1274 (April 11) 1942.

215. Waksman, S. A.: Antagonistic Relations of Microorganism, *Bact. Rev.* **5**: 231-291 (Sept.) 1941.

216. Rammelkamp, C. H.: Observations on the Resistance of *Staphylococcus Aureus* to Action of Tyrothricin, *Proc. Soc. Exper. Biol. & Med.* **49**:346-350 (March) 1942.

217. Weinstein, L., and Rammelkamp, C. H.: A Study of the Effect of Gramicidin Administered by the Oral Route, *Proc. Soc. Exper. Biol. & Med.* **48**: 147-149 (Oct.) 1941.

218. Neter, E.: Effects of Tyrothricin and Actinomycin A upon Bacterial Fibrinolysis and Plasma-Coagulation, *Proc. Soc. Exper. Biol. & Med.* **49**:163-167 (Feb.) 1942.

219. Schoenbach, E. B., and Seidman, L. R.: A Selective Medium for Isolation of *Hemophilus Influenzae*, *Proc. Soc. Exper. Biol. & Med.* **49**:108-110 (Jan.) 1942.

A new substance, streptothricin, isolated from a soil Actinomyces, has been found to inhibit the growth of gram-negative bacteria like *Escherichia coli* and of gram-positive ones like *Bacillus subtilis* and micrococci.<sup>220</sup> It also is bactericidal for gram-negative bacteria.

In therapeutic trials<sup>221</sup> in 12 cases of various types of infection tyrothricin apparently caused local beneficial effects in 6 and was of doubtful value in the rest. In cases like these it is not always easy to provide adequate controls. In a further study<sup>222</sup> on more patients the same authors report that of 50 cases, the results were good in less than half, fair in 25 per cent and poor in 32 per cent.

English investigators<sup>223</sup> report further studies on penicillin, a similar antibiotic agent produced by the mold *Penicillium*. They describe the technic for its isolation and preparation for clinical use. In test tube experiments the bacteriostatic effect of penicillin on streptococci and staphylococci was greater than that of sulfanilamide compounds. Penicillin unlike the drugs was not antagonized by pus when applied to wounds. It had no harmful effect on leukocytes. In clinical trials both by intravenous injection and by local application the authors report favorable effects, but many more studies are necessary to determine the actual value of penicillin as a therapeutic agent and its possible harmful side effects.

*Immune Reactions.*—When normal globulin or other protein is subjected to the action of denaturing reagents or conditions in the presence of an antigen, the protein molecule unfolds and then refolds in such a way as to acquire the properties of a specific homologous antibody. In this ingenious manner Pauling and Campbell<sup>224</sup> have for the first time been able to produce specific antibodies in vitro.

Although fever has long been regarded as an attempt on the part of the body to combat infection and has led to the use of artificially induced fever as a method of treating certain infectious diseases, Ellingson and Clark<sup>225</sup> now show that hyperpyrexia causes a significant lowering of

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220. Waksman, S. A., and Woodruff, H. B.: Streptothricin, a New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria, *Proc. Soc. Exper. Biol. & Med.* **49**:207-210 (Feb.) 1942.

221. Herrell, W. E., and Heilman, D.: Experimental and Clinical Studies on Gramicidin, *J. Clin. Investigation* **20**:583-591 (Sept.) 1941.

222. Herrell, W. E., and Heilman, D.: Further Experimental and Clinical Studies on Gramicidin, *J. A. M. A.* **118**:1401-1402 (April 18) 1942.

223. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Hcatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin: Growth, Assay, Production, Bacteriostatic Action, Effects on Cells, Absorption, and Excretion, and Therapeutic Trial, *Lancet* **2**:177-189 (Aug. 16) 1941.

224. Pauling, L., and Campbell, D. H.: The Production of Antibodies in Vitro, *Science* **95**:440-441 (April 24) 1942.

225. Ellingson, H. V., and Clark, P. F.: The Influence of Artificial Fever on Mechanism of Resistance, *J. Immunol.* **43**:65-83 (Jan.) 1942.

the specific antibody titer and perhaps actual destruction of antibodies in experimental animals. In spite of this untoward evidence, the effect of temperature at fever levels on the destruction of certain bacteria, the increase in the circulation of blood, the changes in the viscosity of blood, the increased activity of phagocytes and other factors still indicate the value of fever in combating infections. There is, of course, a great difference in the effect of "genuine" fever as the result of infection or the presence of foreign protein in the body as compared with that of fever produced by heating the body artificially or by raising the temperature by preventing radiation of normally produced heat. Fever caused by infection makes far more profound changes in the body than the mere elevation of temperature by other processes.

Goodner <sup>226</sup> has devised a supersensitive specific immunologic test employing the principle of collodion fixation. The test is reported to be about a thousand times more delicate than any heretofore described immune reaction and may eventually be of value in the identification of filtrable viruses.

Tsao <sup>227</sup> showed that the administration of estrogens from the urine of pregnant women increased and maintained the bactericidal property of the blood serum of adult male rabbits against *Eberthella typhi* as long as three hundred days. It was not determined if this effect was a direct response to the estrogen or was due to changes in the body.

Freeman <sup>228</sup> investigated a peculiar phenomenon concerning the lack of immunity of mice to a latent virus, habitually carried by them. The host-virus relation seemed to be stable until disturbed by some procedure which reduced resistance. The virus then became invasive, killing all the mice that became sick. Mice inoculated deliberately with the virus and some inoculated intranasally with sterile physiologic solution of sodium chloride became sick, but on retest they were all again susceptible to infection. Uninoculated cagemates of sick and moribund mice did not contract the disease and were not immune. Immune serum prepared in rabbits failed to protect against infection. These apparent paradoxical facts seem to parallel certain observations on human beings, particularly in studies on herpes simplex or on influenza in which demonstrable immune bodies do not seem to protect certain patients from infection.

Jefferson Medical College.

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226. Goodner, K.: Collodion Fixation: A New Immunological Reaction, *Science* **94**:241-242 (Sept. 5) 1941.

227. Tsao, S. N.: Bactericidal Property of Blood Serum of Male Rabbits Treated with Urinary Estrogens, *Proc. Soc. Exper. Biol. & Med.* **48**:38-40 (Oct.) 1941.

228. Freeman, G.: Lack of Immunity to Latent Virus, *Proc. Soc. Exper. Biol. & Med.* **48**:568-570 (Dec.) 1941.

## News and Comment

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**American College of Physicians.**—The American College of Physicians will hold its twenty-seventh annual session in Philadelphia, April 13 to 16, inclusive, 1943. In the interest of conserving time and money for members, the program will be condensed into four days, Tuesday through Friday, instead of extending over the usual five days. Dr. James E. Paullin, Atlanta, Ga., president, will have charge of the general sessions and lectures; Dr. George Morris Piersol, Philadelphia, general chairman, will be responsible for the hospital clinics, panel discussions, local arrangements and entertainment, and the general management of the session and the technical exhibits will be handled by the executive secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia.

Other medical societies are urged to avoid conflicting dates for mutual benefit.

**American Association for the Advancement of Oral Diagnosis.**—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be "The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

**Chicago Society of Internal Medicine.**—At the annual meeting of the Chicago Society of Internal Medicine, held May 25, 1942, the following officers were elected: LeRoy H. Sloan, president; Italo F. Volini, vice president; Richard B. Capps, secretary-treasurer, and Howard L. Alt, secretary-treasurer pro tem.

## Book Reviews

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**Psychosurgery: Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders.** By Walter Freeman, M.D., Professor of Neurology, and James W. Watts, M.D., Assistant Clinical Professor of Neurosurgery, George Washington University. Price, \$6. Pp. 338, with 81 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

This is one of the most interesting and important books of the year because it marks the first major development in the treatment of mental disease since the advent of shock therapy. A new operation for certain types of psychoses and neuroses is described in minute detail in part III. Briefly, the procedure consists in making a burr hole in the skull over the premotor area of the frontal lobe. A flat blade shaped like a spatula is inserted 5 cm. into the brain and given a pendulum-like movement, so that it severs most of the fiber tracks which traverse the white matter at this level. The operation is performed on both sides at one sitting. The net result is a partial but permanent separation of the frontal lobes from the rest of the brain. An operation of this type was first performed in 1935 by Egas Moniz, to whom the book is dedicated. The authors report their experience with a modified operation in 80 consecutive cases of mental disorder.

Although the authors concede that the frontal lobes are essential for satisfactory social adaptation, they suggest that mental disorder may be due to perverted activity of these lobes and that therefore a person may become better adapted if the lobes are partially inactivated. The obvious corollary is that without the frontal lobes there could be no functional psychosis. Specifically, the partial separation of the frontal lobes from the rest of the brain results in reduction of disagreeable self consciousness, abolition of obsessive thinking and satisfaction with performance, even though the performance is inferior in quality. The emotional nucleus of the disorder is said to be removed. Even though fixed ideas may persist and compulsion may continue for a while, the fear that disabled the patient is banished. The authors find that the relief to those persons suffering from doubts, fears, morbid thoughts, hallucinations, delusions and compulsive activities is great.

The operation is reserved for those patients whose outlook is poor, whose response to other treatment is poor and for those who are approaching disability or suicide.

Thirty-eight of the 80 patients were suffering from involutional depression. Twelve had schizophrenia, and 4 had unclassified psychoses. Nineteen other patients were classified as having obsessive-compulsive neuroses and obsessive-ruminative tension states. The remaining 7 had miscellaneous neuroses. Part IV of the book, which deals with a careful analysis of all the cases, can be briefly summarized by saying that in 50 cases the results were satisfactory, in 16 cases they were fair, in 11 cases they were bad and in 3 cases death resulted.

Part II is valuable in itself as a critical analysis of modern knowledge of frontal lobe function. Parts I and V deal with the historical background and the psychopathologic aspects of the study of prefrontal lobotomy.

Whether or not prefrontal lobotomy becomes a universally accepted treatment for mental disorders cannot safely be speculated about for some years to come. Nevertheless, the study of the patients who have already been operated on has contributed tremendously toward the understanding of pathologic mental processes. This book will be enjoyed by every one who has any interest in mental disorders.



**The Pharmacology of Anesthetic Drugs.** By John Adriani, M.D., Instructor in Anesthesia, New York University College of Medicine, Assistant Visiting Anesthetist, Bellevue Hospital. Price, \$3.50. Pp. 86. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This syllabus is obviously a teaching aid and should therefore be evaluated on the basis of experience with it in the training of anesthetists rather than on the impressions obtained by a pharmacologist from a casual perusal. According to the author, the outline is limited to fundamentals and is intended "to acquaint the student anesthetist . . . with pharmacological facts relating to drugs in current use." The amount of information available in this book relating to the pharmacology of volatile and of nonvolatile anesthetics, barbiturates, opium and opium derivatives, atropine, analeptics and nonanesthetic gases, such as oxygen and carbon dioxide, is considerable. Although of necessity dogmatically given, the views are those generally accepted in pharmacologic circles. Certainly no student of anesthesia who has assimilated any considerable part of the information here presented can use these agents without thinking in terms of physiologic mechanisms.

This reviewer has but two criticisms to offer. At times some of the information presented, important as it may be, seems to him to be somewhat beyond the experience and training of those persons for whom the manual is intended. An example is the discussion of the modification of the pharmacology of morphine by alteration of the hydroxyl groups, as by methylation or acetylation. The same criticism might be made of the presentation of the chemistry of atropine and its relatives or of the pharmacology of parasympathetic action. A second criticism, also not too important, has to do with the general form in which the material is presented. Extensive use is made of conventionalized diagrams. For example, on many pages there is a human figure in outline with certain structures indicated diagrammatically—stomach, colon, liver, bladder, etc. The facts regarding the actions of the drug under discussion are condensed into small paragraphs on the margins of the page, with dotted lines to those parts of the body involved. Even though this book is a syllabus, this procedure seems rather elementary, considering the nature of the material involved, and in some cases it leads to what are essentially inaccuracies of fact. For example, under "Atropine, lungs" occurs the comment "oxygen consumption increased," with a dotted line to the lungs.

The volume is attractively arranged and printed. There are a fairly extensive bibliography and a complete index.

**Breathing Capacity and Grip Strength of Preschool Children.** By Eleanor Metheny, Ph.D. University of Iowa Studies: Studies in Child Welfare, volume 18, number 2. Price, \$1.35, paper, and \$1.70, cloth. Pp. 207, with illustrations. Iowa City: University of Iowa, 1940.

This book relates the experiments of Dr. Metheny on breathing capacity and grip strength. The study is divided into four sections, namely, (1) Problem and Data, (2) Breathing Capacity, (3) Grip Strength and (4) Health Relationships. Each of these sections is fully discussed, with excellent charts and illustrations. At the close of each section is a complete summary. Dr. Metheny describes some new designs for the spirometer and the dynamometer which permit high reliability in measurements.

Grip strength and breathing capacity determinations were done on some 169 children from 2½ to 6 years of age. The results of these tests were analyzed in relation to anthropometric measurements. The grip strength was found superior in girls. No difference was noted when children were compared from the social and the mental standpoint.

Dr. Metheny's work does suggest that prior to the onset of a cold there is a decrease in strength and breathing capacity. If this is so, which does require further proof, it may prove a valuable contribution.

At the close of this book is a list of one hundred and thirty-one references.

The book should serve as a valuable reference guide on this important subject, namely, breathing capacity and grip strength of the preschool child, also for other age groups.

**The Lymphatic System, Its Part in Regulating Composition and Volume of Tissue Fluid: The Lane Medical Lectures.** By Cecil K. Drinker, M.D. Price, \$2.25, cloth, \$1.50, paper. Pp. 101, with illustrations. Stanford University P. O., Calif: Stanford University Press, 1942.

This group of the Lane Medical Lectures continues the high quality of the former ones. The lectures are divided into five parts, "Physiological Principles Displayed in the Evolution of the Mammalian Circulation," "Establishment and Characteristics of the Capillary Circulation," "Appearance and Elaboration of Lymphatic Vessels," "Blood, Tissue Fluid and Lymph, as Illustrated by Experiments Upon the Heart and Lungs" and "Relations of the Lymphatic System to Practical Problems in Surgery and Medicine."

The material is delightfully presented, with the important data condensed in a few pages. Many contributions of historical significance are included in the discussions. There are many interesting illustrations and a fairly good bibliography. The fifth portion of the lectures is of practical value to all clinicians. The first part of the lectures is of interest to students of circulatory phenomena as well as to clinicians. The reviewer only regrets that he was not present to hear the lectures presented by Dr. Drinker, who has made many important contributions to the understanding of the functions of the lymphatics.

**Annual Review of Physiology.** By James Murray Luck and Victor E. Hall. Vol. IV. Pp. 709. Stanford University P. O., Calif.: American Physiological Society and Annual Reviews, Inc., 1942.

It is difficult to imagine any physician so industrious as to be able adequately to keep up with all the advances which are made in medical science each year, no matter how systematically he uses his time. This is true of each branch of medicine, but especially true of internal medicine. Much of an internist's daily work is concerned with normal physiologic function and with deviations from normal function. Hence, a volume which furnishes him with a critical summary of a year's work in this field is especially welcome and fills a definite need.

The present volume is edited by a committee of the American Physiological Society, composed of men who are especially well qualified to select those contributions worthy of comment and to prepare each of the twenty-three sections devoted to particular fields of physiology. The bibliographic references are complete, and there are adequate author and subject indexes. The volume is practically indispensable for those persons interested in internal medicine and its advances.

**Tumores primitivos malignos bronco-pulmonares.** By Julio Palacio and Egidio S. Mazzei. Pp. 341, with 129 illustrations. Buenos Aires: El Ateneo, 1940.

This monograph can be said to be one of the most excellent pieces of work ever written on that particular subject.

It is divided into three main parts: (a) bronchopulmonary carcinomas, (b) sarcomas and (c) pulmonary lymphogranulomatous lesions.

The first division takes up almost the whole volume and is really the part the brilliance of which makes the monograph outstanding.

The subject has been presented with complete thoroughness from the point of view of diagnosis, and the illustrations are numerous and well chosen; several colored plates add to the understanding of the text. Little is said as to treatment, and the only opinion expressed is that the present forms of therapy serve more as means of prolonging life, since the proportion of cures is so small. Of particular note is the bibliography, which is complete and represents a great deal of work.

**Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation.** By Bernhard Zondek. Price, \$4.50. Pp. xxiv + 264, with illustrations. New York: Williams & Wilkins Company, 1941.

This monograph, a valuable contribution by an outstanding investigator and clinician, contains a summary of the author's clinical and experimental investigations, together with a résumé of the most important work on the endocrine aspects carried on by other investigators. The text is well written, and the illustrations are excellent. The material contained in this volume is authentic, exhaustive and especially interesting to clinicians, endocrinologists, physiologists and research workers. This volume is heartily recommended to any one interested in the field of endocrinology.

**La protidemia: su valor clinico.** By Aron Gorodner. Thesis. Pp. 143. Buenos Aires: Aniceto Lopez, 1941.

The author has determined the albumin and globulin content of the blood serum in a number of patients suffering from a variety of diseases. The data he presents are limited in value because factors affecting the level of the blood proteins are many; the author considers only one, the disease per se, without regard for its severity, duration or complications. It seems to the reviewer that the chief purpose of the thesis has been achieved in its compilation: The author has learned much about the blood proteins and has demonstrated that knowledge to the satisfaction of his faculty.

**Trastornos cardiacos en los estados anemicos.** By Eugenio R. Pietrafesa. Pp. 209, with 127 illustrations. Buenos Aires: El Ateneo, 1941.

Clinical observations and comprehensive research on rabbits are the basis of this study of the cardiac conditions seen frequently in patients with anemia.

Nothing new is added to what is already known in the correction of these conditions.

The arrangement of the material makes reading somewhat difficult and uninteresting.

**Wounds and Fractures.** By H. Winnett Orr. Price, \$5. Pp. 270, with 137 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book seems especially suitable for general practitioners or surgeons, since it takes up the subject not only by general discussion but by means of many case histories amplified by excellent illustrations. The material is well arranged and should be especially useful today when wounds in combat or civilian injuries may be encountered at any time.

# ARCHIVES of INTERNAL MEDICINE

VOLUME 70

AUGUST 1942

NUMBER 2

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## STAPHYLOCOCCIC PNEUMONIA OCCURRING DURING AN EPIDEMIC OF INFLUENZA

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During the late fall and early winter of 1940-1941 an epidemic of influenza involved most sections of the United States, as well as the Hawaiian Islands, Puerto Rico and probably many other areas.<sup>1</sup> Virus isolations during the acute phase and immunologic studies of acute and convalescent phase serums on patients from widely scattered localities indicated that the virus of influenza A was by far the predominant, if not the only, one of the known viruses implicated in the epidemic.<sup>2</sup> If one

Presented in part at the Fifty-Sixth Session of the Association of American Physicians, Atlantic City, N. J., May 6, 1941.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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(Footnote continued on next page)

judges from the available reports, the disease generally was mild and pulmonary complications were neither frequent nor severe.

The epidemic reached Boston late in December and persisted throughout January; most cases of the disease occurred during the first two weeks of the latter month. The clinical features of some of the uncomplicated cases, along with the results of virus isolations and immunologic studies, have been reported by Pearson, Eppinger, Dingle and Enders.<sup>2e</sup> In the course of the epidemic in Boston an unusually large number of cases of staphylococcic pneumonia were encountered as a complication of influenza. The more important clinical and laboratory data in these cases will be presented here. A more detailed description of the pathologic observations in 8 of the cases included here is given elsewhere.<sup>3</sup> In a recent paper from another Boston hospital, the literature was reviewed and 5 cases were reported which are similar to some of those to be described here.<sup>4</sup> Serologic evidence of infection with influenza A virus was obtained in 3 of those cases. Four fatal cases were also reported from North Carolina.<sup>5</sup>

#### CLINICAL MATERIAL

In all of the cases included in this report the patients were over 14 years of age and were treated at the Boston City Hospital, with the exception of 2 in which the patients were treated elsewhere and which are included because they were of especial interest. In every patient *Staphylococcus aureus* was obtained as the only or the predominant organism from one or more cultures of sputum or from the lungs, or it was obtained in pure culture from blood or from pleural or other exudates or from multiple sources. Virus studies were carried out only in a few of these cases, and the results have been included in the report by Pearson and associates.<sup>2e</sup> Thorough bacteriologic studies were not carried out on all of the patients admitted to the hospital with infection of the respira-

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tory tract during this period, so that many cases with similar clinical features are not included. This presentation is limited to the cases in which adequate bacteriologic data were obtained.

All of the *Staphylococcus* strains were classified as *Staph. aureus* and gave a positive coagulase reaction. Additional studies were made with sixteen of the strains, including eleven from sputum, three from pleural fluid and two from abscesses of the lung. All of them fermented trehalose and mannitol. Uniform suspensions showed more marked agglutination and in higher dilutions in group A serums than in group B serums.<sup>6</sup> The strains varied considerably in the production of alpha and beta toxins, and they probably produced little or no leukocidin, although results of tests for this substance were not conclusive. Mouse inoculation of sputum was not carried out in most instances, because pneumococci were rarely identified in the direct (Neufeld) sputum typings and smears stained with Gram's stain showed abundant organisms resembling staphylococci. In 19 cases, however, sputum which yielded *Staphylococcus* as the only or the predominant organism in direct cultures was also inoculated into mice. The sputum strains of *Staphylococcus* in 10 cases proved virulent for mice when given in this manner, while those in the other 9 cases proved totally avirulent. The latter 9 cases included 3 in which *Staph. aureus* was predominant in cultures of the lungs made at autopsy, 3 in which pure cultures of this organism were obtained from purulent pleural fluid, 1 in which a large staphylococcic pulmonary abscess was evacuated surgically, 1 in which the blood culture was positive for *Staph. aureus* and 1 in which the organism was obtained only from sputum.

The onset of influenza-like symptoms in every case in which the date could be elicited occurred between December 20 and January 18, and in more than three fourths of the cases it occurred between December 25 and January 12. Symptoms suggesting pulmonary infection began on the same day as those of the influenza in about one third of the cases and within five days in another third of the cases, while in the rest they were delayed six days to three weeks. The extent and severity of the pulmonary involvement varied markedly in different cases. In order to bring out the wide variety of clinical features presented in these cases, we have divided them into six main groups, each of which includes a number of cases with more or less distinctive features. For purposes of brevity the important details in three of the groups of cases are presented in tables 1, 2 and 3; the general characteristics of each group will be summarized in the text.

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## ACUTE RAPIDLY FATAL PNEUMONIA (TABLE 1)

In the first group there were 7 cases, in all of which the patients had a more or less fulminating pneumonia following symptoms of moderate or severe influenza. Five patients were in their forties; 1 was 19, and the other, 65. In 1 case (7) the symptoms of pneumonia and of influenza began almost simultaneously; in 4 other cases the patients had been ill with influenza for two to four days without improvement when the pneumonia began, while in 2 cases (1 and 5) the patients had been afebrile for three and nine days, respectively, after the influenza. At the time when the pneumonia was presumed to begin the patients had an abrupt recurrence and marked exacerbation of their prostration, which rapidly changed to a state of semistupor and was associated with severe and increasing dyspnea and cyanosis. The temperature at this stage varied from 100 to 105 F.; the pulse rate, from 120 to 160 per minute, and respirations, from 30 to 40 or more per minute. The latter were usually rapid and shallow, but sometimes they were markedly irregular. Signs in the lungs were minimal at first and consisted then mostly of scattered sibilant and sonorous rales, but as the dyspnea and air hunger increased, showers of consonating rales were heard and there appeared scattered areas of consolidation, which seemed to spread and involve most of the lungs. The patients became apathetic, then stuporous and semicomatose and assumed a "livid" appearance. The leukocyte count in case 1 was 800 on two occasions; in the other cases it varied between 6,100 and 14,000. Death occurred within five days after the onset of the pneumonia in 6 cases and on the ninth day in 1 case.

In 2 cases pleuritic pain was an early and prominent symptom. In both of these cases signs of fluid developed, which was later demonstrated, either by thoracentesis or at autopsy, and found to be infected with staphylococci. The sputum in all the cases was usually raised with difficulty and was scant, thick, purulent and either streaked or diffusely tinged with blood. In case 6 a fibrinous, gray-green, blood-streaked mass of sputum was raised which resembled a diphtheritic membrane but which yielded an abundant growth of *Staph. aureus* in pure culture.

Autopsies were performed in 4 of the 7 cases.<sup>3</sup> All showed diffuse necrotizing bronchitis and bronchiolitis with numerous small and confluent abscesses around the bronchi and massive confluent areas of hemorrhagic and edematous bronchopneumonia. In case 1 the process was more acute and involved mostly the lower and the middle lobe of the right lung, and no abscesses were recognized grossly. Histologically, however, there were edema and necrosis of bronchial and alveolar walls, although the exudate contained little fibrin and few inflammatory cells. Masses of cocci were seen in the necrotic areas in all of these

TABLE 1.—*Relevant Data in Seven Cases of Fatal Acute Staphylococcal Pneumonia Complicating Influenza*<sup>†</sup>

Case No.	Sex and Age, Yr.	Dates			Bacteriologic Data			Chemotherapy		Comment on Clinical Course and Autopsy†
		Hospital Admission	Onset of Influenza	Onset of Pneumonia	Death	Sputum	Blood	Other Sources	Drug	
1†	♀ 46	1/0 1 a.m.	1/3	1/8 10 a.m.	1/9 3:30 p.m.	1/9, G+ cocci	1/9, 0	HB, 0; LL, RL and RU, SA	ST <sup>‡</sup>	WBO 800; fulminating course, increasing dyspnea, cyanosis, stupor; autopsy: acute hemorrhagic and edematous confluent bronchopneumonia, mostly RL and RM, with emphysematous blebs; ? hyaline alveolar membrane; necrotic alveolar and bronchiolar walls and coeli, bone marrow hyperplasia (granulocytes)
2	♀ 13	1/11 1 a.m.	1/7	1/9	1/13 1 a.m.	1/11, STG; 1/12, SA (no ST)	1/11, ST	HB and Per, 0; liver and spleen, SA; RL and abs., LL, SA; LL and PF, SH and SA	ST <sup>‡</sup> NaSD SD	WBO 11,000; increasing dyspnea, cyanosis and pulmonary involvement; autopsy: all lobes with acute necrotizing bronchitis and bronchiolitis and alveolitis, military abscesses, mostly peribronchial but some confluent, scattered hemorrhage and edema and coeli; virus influenza A in lung (indirect); 1/11, CFA 1:16
3	♂ 16	1/13 10 p.m.	1/9	1/13 a.m.	1/16 6 p.m.	1/16, SA, few SV	1/11, 0	HB, 0; RL and LL, SA, few SV	ST <sup>‡</sup>	WBO 6,300; mild diabetes, controlled with insulin; increasing prostration, dyspnea, cyanosis, pulmonary consolidation; autopsy: same as case 2
4	♂ 6½	1/13 9 p.m.	1/6	1/9	1/11 2 p.m.	..	1/13, 0	Lungs, PF and Per, SA	ST <sup>‡</sup>	Dyspnea, pleurisy, cyanosis, restlessness, increasing air hunger; autopsy: 700 cc. turbid yellow fluid in right pleura, 75 cc. in pericardium, myocardial hypertrophy (100 Gm.), healing pulmonary infarct RU, congestion of liver; lungs as in case 2
5	♂ 19	1/12 11 p.m.	12/30	1/12 5 p.m.	1/11 9 p.m.	1/13, SA, few SV	1/13, SA 1/11, SA	.....	SD	WBO 12,000; improvement after 3 days' "flu"; sudden prostration, cough, sore throat, pleurisy on left side, friction rub LL, consolidation extending through LL, LU and RL; increasing dyspnea, cyanosis and stupor; no autopsy
6	♀ 19	1/1 1 p.m.	12/31 11 p.m.	1/2 7 p.m.	1/6 10 a.m.	1/5, SA (wtsec)	1/1, 0	.....	NaSD SD	WBO 6,100; chills, irregular labored respiration, hoarseness, presternal pain, rose-colored fibrinopurulent sputum, bronchitis and bronchiolitis; increasing cyanosis, air hunger and pulmonary consolidation; no autopsy
7	♂ 18	12/28 5 a.m.	12/22	12/22	12/31 1 p.m.	12/28, SA 12/30, SA 12/31, SA	12/28, 0 12/29, 0 12/30, 0	12/30, PF, SA	SP	WBO 13,700; chills, fever, pleurisy on left side; scattered musical and crepitant rales; 10 cc. purulent pleural fluid by thoracentesis; increasing dyspnea, cyanosis and "collapse"; no autopsy

\* The following abbreviations are used throughout tables 1, 2 and 3: G+, gram-positive; SA, Staph. aureus; SH, Streptococcus haemolyticus; SV, Str. viridans (or alpha hemolytic streptococci); 0, no growth in a culture; HB, heart blood; LL, lower lobe of the left lung; LU, upper lobe of the left lung; RL, lower lobe of the right lung; RM, middle lobe of the right lung; RU, upper lobe of the right lung; abs., abscess; PF, pleural fluid; Per., pericardial fluid; ST, staphylococci; NaSD, sodium sulfadiazine; SD, sulfadiazine; SP, sulapyridine (2-[paraaminobenzenesulfonamido]-pyridine); WBO, leukocytes per cubic millimeter, and CFA, complement fixation test with influenza A virus (serum dilution).<sup>26</sup>

† For more detailed autopsy observations in cases 1 through 4, see the corresponding case numbers in the paper by Volkmann and Finland.<sup>3</sup>

‡ Drs. George E. Currier, Sidney C. Dalrymple and Dwight O'Hara, of Waltham Hospital, gave us permission to report the data in case 1.



cases. Hyaline-like membranes similar to those described in the influenzal pneumonias of 1918<sup>7</sup> were seen, particularly in case 1.

*Staph. aureus* was the only or the predominant organism obtained from the various cultures made during life and at autopsy. Small numbers of *Streptococcus viridans* were also obtained in 2 cases. In case 2 the first cultures of sputum and of blood showed hemolytic streptococci, but on the following day only staphylococci were obtained from the sputum. At autopsy in this case culture of heart blood showed no growth. Staphylococci were grown alone from some sites and with hemolytic streptococci from others (table 1). In the microscopic sections of the lungs, chains of cocci were seen in some hemorrhagic and edematous areas of intact alveoli, while masses of cocci were seen in abundance in the necrotic areas. Ferret inoculation of a suspension of lung in this case yielded strong presumptive evidence of the presence of influenza A virus.<sup>2a</sup>

FATAL ORGANIZING AND FIBROSING PNEUMONIA  
(TABLE 2 AND FIGS. 1 AND 2)

In a second group of 6 cases the patients had a clinical course similar to that in the first group except that the patients survived from fifteen to fifty-six days after the onset of severe pulmonary symptoms. In all of these cases the patients were 50 years of age or older, and in 3 they were over 70. The pneumonia began almost simultaneously with the influenza in 4 cases, but in 1 the patient apparently enjoyed a full week without symptoms between the influenza and the pneumonia. In 2 cases (9 and 11) there was a temporary remission of fever and slight improvement after a few days of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) therapy.

The outstanding feature of all these cases was the persistent and intense dyspnea and cyanosis, which were only slightly affected by oxygen administration. The patients were irrational and stuporous most of the time. Signs of diffuse bronchitis and of scattered patches of consolidation were present throughout the lung but were usually more extensive in one or two lobes. Signs of extensive cavitation suggestive of advanced pulmonary tuberculosis were made out clinically and by

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TABLE 2.—Clinical and Laboratory Data in Six Cases of Fatal "Chronic" Fibrosing Staphylococcic Pneumonia Complicating Influenza †

Case No.	Sex and Age, Yr.	Dates			Bacteriologic Data			Chemotherapy		Comment on Clinical Course and Autopsy †
		Hospital Admission	Onset of Influenza	Onset of Pneumonia	Death	Sputum	Blood	Other Sources	Drug	
8	♀ 71	1/12	1/5	1/5	1/20	1/15, SA, Pn XVII, SV	.....	HB, 0; RL, SA; III, SV	...	Irrational, severe cough; Paget's disease of skull, auricular fibrillation, B. P. 100/110; WBC 11,600, low grade fever, bilateral patchy consolidation, emphysema; 1/17 improved, sat up; 1/19 irrational, increasing dyspnea, stupor; autopsy: fibrinous pleuritis, pulmonary fibrosis, walled-off abscesses connected with dilated bronchi, mostly in lower lobes; arteriosclerotic heart disease, healed pyelonephritis, Paget's disease of skull and spine
9	♀ 76	1/21	?	1/18	2/9	1/24, SA	1/24, 0 1/27, 0	HB and LL, 0; RU, SA, few HI	SD	"Cold," then prostration and chest pain (poor history); WBC 24,000, dropped gradually to 5,500, then rose to 18,700; NPN 49, dropped to 30; patchy pneumonia RM and RU; extrasystoles; improvement under therapy, then low grade fever, increasing dyspnea, cyanosis and extension of pulmonary involvement; autopsy: bilateral fibrous pleuritis, firm gray fibrosis of lung parenchyma in RU and RM, moderate bronchiectasis, mostly in both lower lobes
10	♀ 50	12/30	12/24	12/24	2/18	1/2, SA, few Pn XIV; 1/7, SA, SV; 1/15, SA, SH; 1/28, SA, SH	2/7, SA, many others before and after, 0	HB, 0; LL and RL, SH and SA; abs. RL, SH and SA	ST	12/24 "grip," coryza, weakness, cough; 12/30 acute air hunger, bilateral bronchitis and patchy consolidation of lower lobes, irregular fever, marked and persistent dyspnea and cyanosis, WBC 9,000 to 18,000; autopsy: hypertrophy and dilatation of right auricle and ventricle, abscesses in myocardium, marked fibrosis, bronchiectasis and thick-walled abscesses in both lungs, few scattered abscesses in liver and spleen and kidneys (temperature chart and roentgenogram of chest shown in figs. 1 and 2)
11	♂ 81	1/26	? 1/5	? 1/5	2/3	1/29, SA, few SV	1/26, 0	RU, 0; RL and LL, SA, few SV	SD	Cough, vomiting (poor history); feeble; bronchopneumonia mainly in RL, fever and pulse rate dropped after SD begun, then rose again; WBC 10,000, rose to 27,000 on 1/28; increasing dyspnea and cyanosis; autopsy: bilateral organizing pneumonia and fibrous pleurisy
12	♂ 64	1/20	1/9	1/19	2/3	1/21, SA, SV	1/20, 0 1/21, 0	.....	SD	Improvement after "grip," then sudden dyspnea, cough, yellow bloody sputum; disorientation; diffuse patchy consolidation; WBC 17,000, dropped to 9,000 on 1/26 and rose gradually to 35,000; irregular temperature to 103 F.; abscess cavities in RU; temporary improvement on SD; thrombophlebitis of right leg 2/1; OFA > 1:128 on 2/2; no autopsy
13	♀ 56	1/7	1/5	1/5	3/1	1/9, SA, few SV, Pn III; neg. for TB 14 times	1/7, SA; many others, 0	.....	ST	Severe cough, substernal tightness while nursing son for "influenza"; fever, prostration, cyanosis, dyspnea, thick yellow sputum; diffuse patchy consolidation, extending to entire lung; many large abscess cavities revealed by roentgen examination; WBC 5,000 to 18,000; right ventricular predominance (cor pulmonale); died with symptoms of cardiac failure; no autopsy

\* In addition to the abbreviations indicated in table 1, the following ones have been employed in tables 2 and 3: Pn, pneumococci, with the type represented by a Roman numeral; TB, tubercle bacilli; HI, Haemophilus influenzae; BP, blood pressure; and NPN, nonprotein nitrogen measured in milligrams per hundred cubic centimeters of blood.  
 † For more detailed autopsy observations in cases 8 through 11, see cases 5 through 8, respectively, in the paper by Wollenman and Finland.<sup>3</sup>



Fig. 1 (case 10).—Bedside roentgenogram of the chest made at the end of the sixth week of illness. Extensive bilateral fibrosis and cavitation (abscesses) are evident, especially in the lower lobes, and the heart is enlarged to the right. For the clinical chart in case 10 see figure 2.

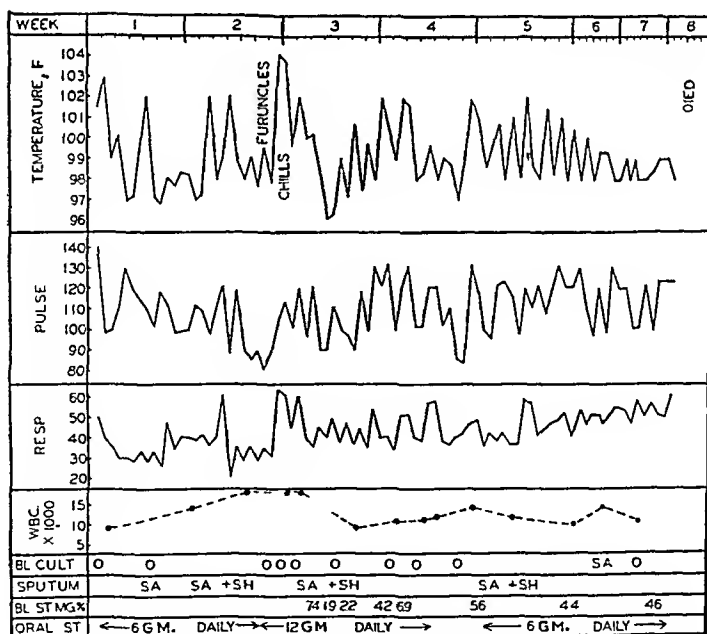


Fig. 2 (case 10).—Clinical chart for M. B., a 50 year old woman admitted to the hospital Dec. 30, 1940, six days after the onset of pneumonia. Under blood culture (BL. CULT.) O signifies the culture was negative for growth. For the other abbreviations see the starred footnote to table 1.

roentgen examination in case 13, but numerous examinations of the sputum failed to reveal tubercle bacilli. In the 2 cases of the longest illness there was evidence of increasing failure of the right side of the heart with marked distention of the cervical veins and engorgement of the liver. In case 10 hypertrophy of the right ventricle and dilatation of both chambers of the right side of the heart were noted at autopsy, and in case 13 enlargement of the right side of the heart was revealed by roentgen examination and the electrocardiogram showed right ventricular predominance.

Autopsies were performed in 4 of these cases,<sup>3</sup> and all revealed similar conditions in the lungs. The bronchi were dilated and filled with exudate, and their walls were necrotic and fibrosed. There were numerous thick-walled abscess cavities, some of which communicated with bronchi or bronchioles, and much of the intervening parenchyma was replaced by fibrous tissue. Some of the uninvolved parenchyma, especially in the upper lobes or at the periphery of the lungs, was emphysematous. The picture was similar, in general, to that of the organizing pneumonias described by Winternitz and associates<sup>7e</sup> and others among the influenzal pneumonias of 1918.

Cultures of sputum and of the lungs showed *Staph. aureus* predominating in every instance, but small numbers of pneumococci and *Str. viridans* were also obtained from sputum, and influenza bacilli were obtained from the lungs in 2 cases. In case 10 hemolytic streptococci appeared in the sputum and persisted; they were later found in the lungs. Blood cultures were positive for *Staph. aureus* on a single occasion in 2 cases; all others, including those made at autopsy, yielded no growth. In 1 of the cases with bacteremia (case 10) multiple miliary abscesses were encountered in the viscera at autopsy. Serologic studies were made in only 1 case in this group (case 12) and showed complement fixation with influenza A virus to a high titer (1:128) on the day before death, which was twenty-four days after the onset of clinical influenza. This may be presumed to be indicative of recent infection with influenza A virus.

#### SEVERE STAPHYLOCOCCIC PNEUMONIA WITH RECOVERY (TABLE 3 AND FIG. 3)

A third group comprises 11 cases in which the symptoms during the early stage of the pulmonary infection were somewhat like those in the fatal cases. The pneumonia in these cases was limited largely to one lobe or to one lung, and improvement gradually occurred under intensive therapy with derivatives of sulfanilamide. The patients in this group of cases were generally younger than those in the preceding groups; with 1 exception they were under 45, and 5 of them 25 or younger. Most of the patients also had diffuse tracheobronchitis.

TABLE 3.—Summary of Clinical and Laboratory Data in Eleven Cases of Severe Staphylococic Pneumonia Complicating Influenza with Recovery \*

Sex and Case No.	Age, Yr.	Hospital Admission	Dates				Discharge	Bacteriologic Data			WBC Range During Fever	Lung Chiefly Involved, Roentgen Examination	Chemotherapy		Comment on Clinical Course
			Onset of Influenza	Onset of Pneumonia	Symptomatic Improvement	Afebrile		Sputum	Blood	Pleural Fluid			Drug	Gm.	
14	♂ 16	12/27	12/20	12/24	1/5	2/13	2/21	12/28, SV (mouse); 1/1, SA	12/27, 28 and 29, 0; 1/1, SA; 1/6, 9 and 14, 0	12/29, 1/1 and 1/3, SA	15,000-20,000	RL, fluid	SD ST	35 112	Scarlatiniform eruption on admission; 250 cc. thin pus removed at each thoracentesis; catheter drainage and lavage with 0.5% NaSt in saline 1/5; rib resection 1/13, thick-walled cavity almost empty; ST rash and fever; CFA negative on 12/25, 3/25
15	♂ 44	1/10	1/9	1/15	1/30	1/28	2/27	1/17, Pn IV (N)	1/16, 0	1/19, 20, 21 and 23, SA	27,000-13,000	RL, fluid	SD	44	Blood-stained white sputum, marked dyspnea, diffuse bronchitis; 80-800 cc. pus removed at each puncture; rib resection 1/23, gradual improvement
16†	♀ 25	1/22	1/3	1/4	3/17	3/17	3/25	1/8, SA; 1/22 and 23, SA, SV	1/22, 0	.....	15,000-23,000	RU, RM; cavities in RU	ST	70	Severe tracheobronchitis, followed by consolidation and large abscess; blood-stained sputum; drained by rib resection 1/23; ST in wound; secondary operation 2/19
17	♂ 57	1/14	1/10	1/13	1/20	2/7	3/12	1/15, SA, Pn XVIII; 1/17 and 25, SA; 2/3 and 12, SA, SV	1/15, 17 and 21, 0	1/16 and 18, SA; 1/20, no fluid	3,000-16,000	RL, fluid	ST SD	106 31	White, blood-streaked sputum; bronchitis and bronchopneumonia; thick, reddish purulent fluid, 200 cc. removed 1/16, 20 cc. 1/20, replaced by 0.5% NaSt in saline; ST rash, 1/30 changed to SD; CFA > 1:64 on 2/15 and 3/1
18	♂ 17	1/6	12/28	1/4	1/10	1/14	1/30	1/8, SV	1/6 and 20, 0	1/8, 12 and 13, SA	17,000-23,000	LL, fluid	SD ST	21 71	Signs of pneumonia followed by those of fluid; 20-180 cc. thick pus removed each time; cleared completely without operation; ST rash and episcleeritis 1/18

19	♂ 14	1/3	12/31	12/31	1/10	1/10	2/1	1/6, Pn VI (N); 1/8 and 12, SA; SV; 1/11, SA	1/3, 6, 7, 9 and 11, 0	1/6, 9 and 15, SA; 1/20, no fluid	17,000- 10,000	LL, fluid	SD	35	Three thoracenteses each yielded 5-10 cc. thick pus; no fluid fourth time; critical drop in tempera- ture; no operation
20	♂ 61	1/10	1/12	1/10	2/6	2/11	3/10	1/20, 21 and 23, SA, few SV; 1/28 and 3/1, SA	1/19, 24, 26, 28, 29 and 30, 0	1/28, 29 and 2/7, 0	15,000- 25,000	Right lung, fluid, ? cavities	SD ST SD	54 83 31	Rusty sputum; recurrent chills; marked prostra- tion; small amounts thin, straw-colored pleural fluid; gradual improvement; signs in lung persisted for 4 mo.; ST rash and epi- scleritis 2/9-2/13; multiple transfusions; CFA 1:33 on 3/1 and 1:4 on 4/15
21	♂ 41	1/12	1/7	1/9	1/13	1/23	2/8	1/12, 15 and 25, SA, few SV	1/12 and 13, 0	1/23, 0	16,000- 4,000	RL, RM, fluid, cavities	SD	100	Mild diabetes, readily con- trolled; marked dyspnea, prostration; brown spu- tum; rapid improvement after SD started; 10 cc. serous fluid obtained once; CFA 1:8 on 1/12 and 1:64 on 3/22
22	♂ 35	1/31	1/8	1/8	2/6	2/10	3/27	2/7, 10 and 3/4, SA, few SV; 2/9 and 3/6, SA, Pn XVIII	1/31, SA; 2/6, 14 and 18, 0	.....	11,000- 19,000	RL, ? eavi- ties; signs of TB in RU	ST	59	Sk weeks' cough before "flu"; RL consolidation cleared, signs in LU per- sisted; sputum neg. for TB; guinea pig inoculated with gastric washing 3/28, pos. for TB; fever 2/21-3/4; ST rash 2/9; CFA 1:64 on 3/22 and 1:16 on 4/28 (fig. 3)
23	♂ 21	1/10	1/7	1/7	1/19	1/27	2/5	1/10, 11, 12 and 17, SA, few SV; 1/28, SA, SH	1/10, 11, 13, 18, 19 and 20, 0	.....	6,000- 16,000	RL, ? fluid or thick pleura	ST SD	25 40	Tracheobronchitis on ad- mission, then consolida- tion RL and ? fluid; jaun- dice on 1/13; IL, 30
24	♂ 38	1/22	1/1	1/10	1/24	2/11	2/18	1/23, SV, HI; 1/25, 28 and 30, SA, SV	1/22, 25, 26 and 28, 0	1/28 and 31, 0	10,000- 17,000	LL, fluid, cavities	SD ST	48 25	Marked improvement after chemotherapy; fever con- tinued, copious brown sputum; 15 cc. thin pleural fluid twice; lung cleared completely

\* In addition to the abbreviations indicated in tables 1 and 2, the following ones have been employed in table 3: (N), direct typing of pneumococci by Neufeld capsule swelling; IL, icterus index; NaSP, sodium sulfathiazole.

† The patient in this case was treated in other hospitals. Dr. Joseph M. Rosenthal permitted us to report the data.

Pleural fluid varying in amount from 10 to 800 cc. was obtained by thoracentesis in 8 cases. The fluid in 3 cases was sterile every time, while in each of the remaining 5 cases an abundant growth of *Staph. aureus* was obtained from the fluid on two or more occasions. In 2 of the latter cases treatment was by rib resection; in the other 3 the condition cleared completely and did not require surgical intervention. In 1 case large abscess cavities in the upper lobe of the right lung were drained through a rib resection and later required a secondary operation

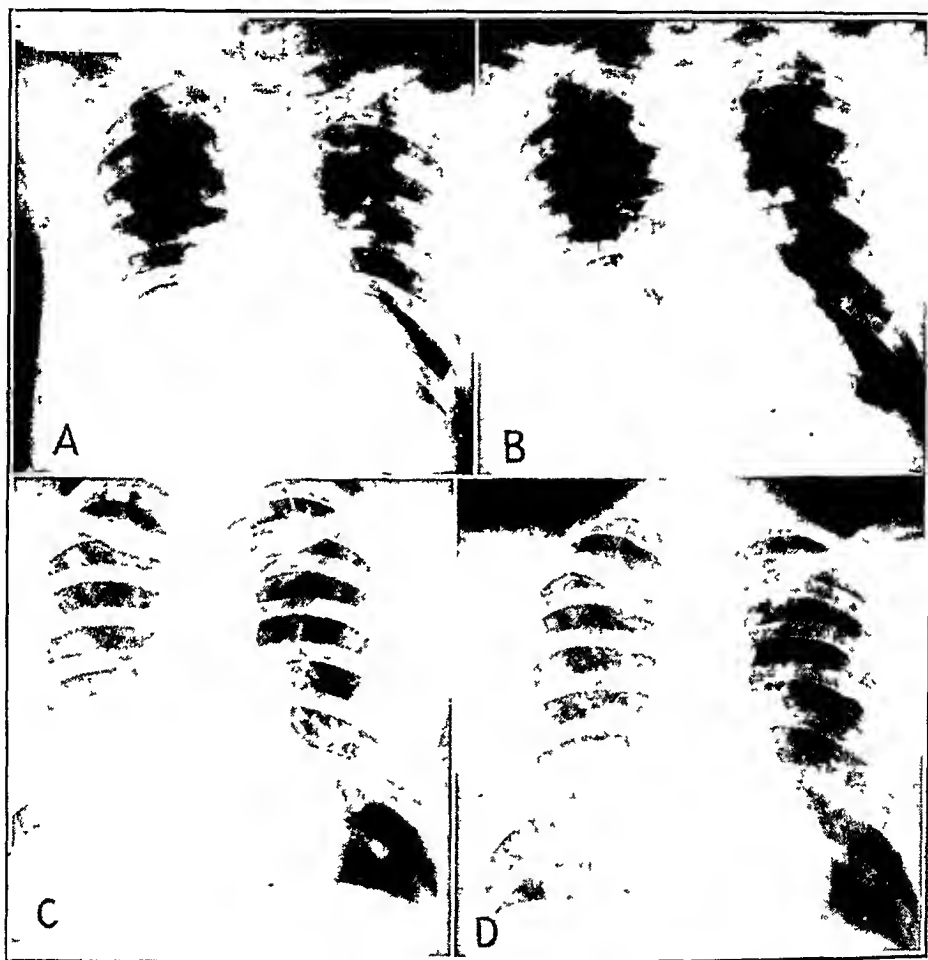


Fig. 3 (case 22).—Serial roentgenograms of the chest, showing essential clearing of the acute process in the right lung and pleura and persistence of the tuberculous infiltration near the apex of the left lung. The roentgenograms were made on (A) Feb. 11, 1941; (B) February 27; (C) March 12, and (D) April 17.

to evacuate an undrained area of suppuration. In at least 2, and probably 4, of the other cases, the patients had areas of abscess formation within the affected lung which were discernible as rarefied areas by roentgen examination. They apparently healed completely, presumably after draining into bronchi, as evidenced by profuse purulent sputum.

The results of culture of sputum in these cases were similar to those in the fatal cases. In each of 2 cases, including 1 in which the patient had infected pleural fluid, a blood culture positive for *Staph. aureus* was obtained on one of several occasions. Complement fixation tests with influenza viruses were done with the serums of 5 patients in this group. In 4 cases the serum showed significantly high titer or more than a fourfold change of titer with influenza A virus. In the fifth case (14) serum examined on the eighth day after the onset of influenza and again three months later gave negative results.

Recovery in these cases was slow, but eventually it was complete as far as could be ascertained. In some of these cases the patients have now been followed up for more than a year and have remained well. Only 2 of the patients became afebrile within ten days of the onset of pneumonia, while in the others fever and other evidences of active infection persisted for two to five weeks. In case 20 roentgenographic signs of fluid persisted for over four months and eventually cleared, leaving evidence of residual pleural thickening and adhesions. One patient (case 22, fig. 3) had a history of cough for six weeks prior to the onset of influenza. In this patient, although the pneumonic consolidation was limited chiefly to the lower lobe of the right lung, where there was also evidence of abscess formation, crepitant rales were heard in the upper lobe of the left lung throughout his stay in the hospital, and there was persistent mottled infiltration in this region in the roentgenograms. The signs in the lower lobe of the right lung cleared slowly and apparently completely, while those in the apical region of the left lung remained unchanged. Sputum smears were negative for tubercle bacilli during the acute illness. No sputum was obtainable later, but material aspirated from the stomach yielded tubercle bacilli on guinea pig inoculation.

#### ACUTE STAPHYLOCOCCIC PNEUMONIA WITH RAPID AND COMPLETE RECOVERY

In the fourth group there were 18 cases, in all of which the patients had symptoms and signs (including roentgenographic evidence) of pneumonia which began between December 30 and January 20, at the same time as or a few days after an attack of clinical influenza. In 13 cases the patients were less than 45 years old, and in 3 they were over 70. *Staph. aureus* predominated in cultures of sputum in every case; *Str. viridans* occurred in most of the cases, and pneumococci of higher types and influenza bacilli were found together in 1 case and separately in others. Blood cultures were positive for *Staph. aureus* in 2 cases and showed no growth in all the others. A sterile pleural effusion was demonstrated in 1 case (33). The serum in this case showed complement-fixing antibodies for influenza A in a significant titer.



The maximum temperature in different cases varied from 101 to 105 F., and the pulse rate, from 100 to 140 per minute; respirations were somewhat rapid, and the leukocyte count at the height of the fever varied between 4,000 and 31,000. Pulmonary consolidation was limited chiefly to one lobe in 10 cases and to two lobes in the others; it appeared by physical signs and roentgen examination to be uniformly distributed throughout most of the involved lobes in 5 cases and as irregular patches in the others. One of the patients, a Negress, had a rash which she thought was "measles" at the beginning of her pneumonia, but this had cleared without residual signs at the time of admission to the hospital.

TABLE 4.—*Summary of Some of the Relevant Data in Sixty-Six Cases of Staphylococcal Infection of the Lungs Complicating Clinical Influenza\**

Group †.....	I	II	III	IV	V	VI(a)	VI(b)	VI(c)	Total
Number of cases.....	7 (7)	6 (6)	11	18	4	7 (6)	3	10 (2)	66 (21)
Age, years									
14-39.....	1 (1)	..	8	9	3	..	3	5	29 (1)
40-59.....	5 (5)	2 (2)	2	6	1	2 (1)	..	2	20 (8)
60 and over.....	1 (1)	4 (4)	1	3	..	5 (5)	..	3 (2)	17 (12)
Positive blood culture									
Staph. aureus.....	1 (1)	2 (2)	2	2	..	1 (1)	3	0	11 (4)
Other organisms.....	1 (1)	..	..	..	..	..	..	4	5 (1)
Pleural fluid									
Sterile.....	..	..	3	1	..	..	1	1	6
Infected (with staphylococci).....	3 (3)	..	5	..	..	..	..	1	9 (3)
Chemotherapy									
Sulfathiazole.....	3 (3)	2 (2)	2	5	2	3 (3)	1	3	21 (8)
Sulfadiazine.....	2 (2)	3 (3)	3	11	1	..	1	6 (2)	27 (7)
Sulfathiazole and sulfadiazine.....	1 (1)	..	6	..	..	..	1	1	9 (1)
Sulfapyridine.....	1 (1)	..	..	1	..	1 (1)	..	..	3 (2)
None.....	..	1 (1)	..	1	1	3 (2)	..	..	6 (3)

\* The figures in parentheses represent the number of cases of fatal infection included.

† Roman numerals have been used to designate the following groups: I, fatal acute and fulminating pneumonia; II, fatal organizing pneumonia; III, severe pneumonia, extensive or with complications; IV, acute pneumonia with rapid recovery; V, influenza with tracheobronchitis (most of the cases in this group were excluded for lack of bacteriologic data); VI (a), staphylococcal infection of the lungs complicating cardiac disease or other pulmonary disease; VI (b), focal infection, and VI (c), staphylococcal superinfection of pneumococcal lobar pneumonia.

In all but 1 of these 18 cases the patients were treated with the usual doses of three derivatives of sulfanilamide from the time they entered the hospital. All, including the 1 who did not receive chemotherapy, were markedly improved within eighteen to forty-eight hours, and all but 2 were completely afebrile within one to four days after admission.

INFLUENZA AND TRACHEOBRONCHITIS

The four groups of cases already described include all those with definite pulmonary consolidation following an attack of clinical influenza in which the Staphylococcus was the only or the predominant organism and was considered to be related to the pulmonary lesion. A fifth and

large group of cases was encountered in which symptoms of influenza were associated with or followed by increased prostration, hoarseness and severe cough accompanied by presternal soreness and production of tenacious, purulent and occasionally blood-streaked sputum. The temperature in these cases was usually high (102 to 104 F.), the pulse rapid (100 to 140 per minute) and the respiratory rate somewhat increased. The leukocyte count was within the normal range (6,000 to 10,000). The only abnormal physical signs elicited in the lungs were numerous musical and occasional fine crepitant rales scattered throughout the lungs; the latter were heard most frequently at the bases. Roentgenograms of the chest were usually read as normal, but close inspection often revealed increased bronchial markings and some areas of fine mottling, especially in the lower lobes. Fever and prostration in these cases lasted five to ten days, with a brief remission in some cases, but the cough and sputum persisted for several days longer. The course seemed to be affected only slightly, if at all, by therapy with either sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine.

This clinical picture was probably the predominant one in the cases of severe influenza which were presumed to be uncomplicated. It corresponded in most respects to the influenza with "bronchiolitis" which Stuart-Harris and his co-workers<sup>8</sup> considered to be the commonest lesion encountered in the influenza epidemic of 1936-1937 in England and which was also described at the same time by Scadding.<sup>9</sup> Blood cultures failed to yield growth in any case. Other bacteriologic studies were carried out in only a few of these cases, and they indicated that the flora in the sputum consisted chiefly of common mouth organisms. In 16 cases that were studied the only or the predominant organisms were alpha hemolytic streptococci in 7 cases, beta hemolytic streptococci in 3, pneumococci (types XIII and XIX) in 2 and *Staph. aureus* in 4. In the last-named 4 cases the patients were young or middle-aged women whose illnesses did not differ in most respects from those caused by the other organisms except that the fever and symptoms persisted somewhat longer and seemed to respond less readily to therapy with a derivative of sulfanilamide. Whether the *Staphylococcus* played any role in the pathologic condition in the lungs in these 4 cases is, of course, open to question.

Serologic studies were made in 1 of the 4 cases in which staphylococci were isolated, and a significant titer of complement fixation with influenza A virus was demonstrated. In 2 other cases in which the

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8. Stuart-Harris, C. H.; Andrewes, C. H., and Smith, W.: *A Study of Epidemic Influenza, with Special Reference to the 1936-7 Epidemic*, Medical Research Council, Special Report Series, no. 228, London, His Majesty's Stationery Office, 1938.

9. Scadding, J. G.: Lung Changes in Influenza, *Quart. J. Med.* 6:425-465 (Oct.) 1937.

clinical course was similar the virus itself was isolated by ferret inoculation of nasopharyngeal washings obtained in the early febrile stage.<sup>2e</sup> Staphylococci were not obtained in these 2 cases, and the course of illness in them was brief and comparatively mild.

#### MISCELLANEOUS CASES OF STAPHYLOCOCCIC PNEUMONIA

There were a variety of other cases of staphylococcic infections of the lung which were encountered during the same period. In the majority of these cases an antecedent history of influenza-like symptoms could be elicited. Some of the important features of these cases may be summarized briefly.

In 5 cases the patients, all over 70 years of age, had chronic cardiac disease, and in 1 case a man aged 50 had chronic bronchial asthma; all of them were admitted to the hospital between January 10 and 27 for an acute exacerbation of their chronic illness associated with an acute infection of the respiratory tract. They all died within ten days and were found to have diffuse bronchopneumonia and congestive cardiac failure at autopsy. The asthmatic patient also had severe bronchiectasis and cor pulmonale. Abundant growth of *Staph. aureus* was obtained from the lungs in each case. This was the only organism recovered in 2 cases, while in the others small numbers of alpha and beta hemolytic streptococci, pneumococci (type XXIX) and *Escherichia coli* were obtained in addition. Culture of heart blood yielded the staphylococcus in 1 instance, but showed no growth in the others. Cultures of sputum were made only in the case of the asthmatic patient and yielded *Staph. aureus* in almost pure culture from several specimens.

In a seventh case a man of 55 was admitted to the hospital during the same period with symptoms of acute pneumonia following typical influenza. There were signs of irregular consolidation limited mostly to the upper lobes, and staphylococci predominated in cultures of several specimens of purulent sputum. Stained smears of the last three of eight specimens examined, however, also showed acid-fast bacilli. The patient's fever and acute respiratory distress subsided after a week, but the lesion in the upper lobes persisted and later had the characteristic roentgen appearance of tuberculous infiltration.

Three cases of focal infections are also of interest. In 1 case the patient was a woman of 31 who four weeks post partum had a breast abscess incised (culture not done); then clinical influenza developed, which was followed in a week by pneumonia of the lower lobe of the right lung. This was complicated, in turn, by a sterile pleural effusion. Cultures of thick purulent sputum on several occasions yielded *Staph. aureus* in almost pure culture, and this organism was also grown from

one of three blood cultures. The patient improved and became afebrile after three days of sulfadiazine treatment, and the lung gradually cleared after showing small areas suggestive of cavities in a roentgenogram. The patient in the second case was a Negress aged 34 who had been in the hospital for several weeks and had recovered successfully from exfoliative dermatitis (due to arsphenamine) and sepsis caused by hemolytic streptococci. In the latter part of December symptoms of influenza and pneumonia developed; *Staph. aureus* was recovered in several blood cultures and was predominant in cultures of the sputum, which also contained some hemolytic streptococci. The patient recovered from this illness after a long and severe course with intensive sulfathiazole and sulfadiazine therapy. In the third case typical influenza developed in a youth of 19 on January 12; he had fever (a temperature up to 104 F.) for five days, after which he improved. On January 22 he had a chill, cough, headache and stuffiness of the nose. When seen two days later he had severe maxillary sinusitis and scattered rales in the lungs. Sputum and nasal secretions yielded *Staph. aureus* in pure culture, and the same organism was obtained from the blood culture. Sulfathiazole therapy was given; drainage of the sinus was established, and the patient made a rapid and uneventful recovery.

#### OBSERVATIONS ON PNEUMOCOCCIC PNEUMONIA IN RELATION TO THE INFLUENZA AND THE STAPHYLOCOCCIC INFECTIONS

A few observations concerning some of the cases of typical lobar pneumonia encountered during the influenza epidemic are worth mentioning, since they are relevant to the subject at hand.

During the first three weeks of January 22 patients admitted to four different medical wards with typical lobar pneumonia associated with the common types of pneumococci gave a history of symptoms of influenza beginning one to ten days before the onset of the pneumonia. In 10 of the 22 patients cultures of sputum showed *Staph. aureus* in abundance, either together with pneumococci from the start or appearing in later specimens at a time when the pneumococci declined in number or could no longer be isolated. Two of these 10 patients died; both had type IV pneumococci and staphylococci in their sputum, and cultures made from the lung of 1 of these patients at autopsy showed both organisms. The other 8 patients had a prolonged course with low grade fever, and empyema developed in 1. The lesions in the lungs and the empyema cleared slowly but completely, although in some there was suggestive roentgen evidence of small cavities in the affected lobes during the course of the disease. Three of these patients had type I, 1 had type VIII and 4 had type III pneumococci in the sputum. One of the patients with

type I and 3 with type III organisms had blood cultures positive for pneumococci, but the pleural fluid obtained from the patient with pneumonia caused by type VIII pneumococci yielded a pure culture of *Staph. aureus*.

While cases of "superinfection" with other organisms in the course of pneumococcic pneumonia are not infrequent,<sup>10</sup> the *Staphylococcus* is not often the cause of such secondary infections. It is found much less frequently than hemolytic streptococci under such circumstances. The high proportion of cases with staphylococci in this brief interval is therefore of added interest. Furthermore, similar cases were noted even before the appearance of influenza, since 3 instances had been recognized in the latter part of November. It is also worth mentioning that only 4 cases of pneumonia caused by hemolytic streptococci were encountered during this epidemic. In 2 blood cultures were positive for such organisms; and in 1 there was associated empyema. In all four cases recovery followed sulfadiazine treatment.

Other indirect evidence of infection with influenza A virus in cases of typical pneumococcic pneumonia was obtained from the serologic studies of Pearson and his co-workers.<sup>20</sup> They carried out complement fixation tests with influenza viruses on the serums obtained in a number of cases of classic lobar pneumonia due to common types of pneumococci and found titers of influenza A antibodies which were significantly high or which showed sufficient change to suggest recent infection with this virus. There was no evidence of infection with influenza B virus. The serums were originally collected for the purpose of studying the development of pneumococcus antibodies in cases of pneumonia in which treatment was with sulfathiazole and sulfadiazine. Type-specific pneumococcus antibodies were demonstrated during convalescence in almost all of these cases.<sup>11</sup> Of the patients admitted to this hospital during January, virus studies were made on 16, and the results suggested influenza A infection in 11, or 69 per cent. In the preceding and succeeding months the percentage of such positive results was considerably smaller.

#### SUMMARY AND COMMENT

We have presented the important features of 66 cases of staphylococcic infection of the lungs complicating clinical influenza in adults. In all cases the onset of symptoms of influenza occurred during the period of four weeks when the epidemic was prevalent in and around Boston.

10. Finland, M.: The Significance of Mixed Infections in Pneumococcic Pneumonia, *J. A. M. A.* **103**:1681-1686 (Dec. 1) 1934.

11. Finland, M.; Strauss, E., and Peterson, O. L.: Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole, *Ann. Int. Med.* **16**:1-16 (Jan.) 1942.

Taken together, these cases offer a sort of panorama of the variety of forms in which the *Staphylococcus* manifested itself in the respiratory tract of patients with influenza during this outbreak.

Some of the more relevant data are summarized in table 4. All age groups were represented. Cases of such infection occurring in infants and children were not included, but a number of such patients with pneumonia having bacteremia and empyema caused by *Staph. aureus* were treated in the hospital during this period, and some of the infants died. Among the 66 adults the deaths occurred predominantly in patients over 60 years old, but the fatalities in the acute fulminating infections occurred mostly in middle-aged people. There were 21 deaths in all, a mortality of 32 per cent. Actually, the mortality probably was lower, since many more cases of influenza with minimal signs in the lung (group V) might have been included had more complete bacteriologic studies been made in all such cases.

Blood cultures positive for *Staph. aureus* were obtained in 11 cases, in 4 of which the patients died. Hemolytic streptococci were obtained from the blood in 1 case of fulminating disease, and pneumococcic bacteremia was demonstrated in 4 cases of lobar pneumonia in which there were mixed infections or a superinfection with staphylococci. Pleural effusions were encountered in 15 cases. These proved to be sterile in 6 cases, while cultures of pleural fluid in the other 9 yielded *Staph. aureus*. In 2 of the 9 cases the fluid was discovered at autopsy.

The virus studies carried out by Pearson and his associates<sup>2e</sup> indicated that influenza A played a role in this epidemic and in these cases. The virus was isolated in 2 cases of uncomplicated influenza and was presumptively demonstrated in the lung in 1 of the acute and fatal cases. Immunologic evidence of infection with influenza A (and not influenza B) was obtained in 7 cases and was also demonstrated in 3 of the 5 cases of staphylococcic pneumonia that were encountered during this epidemic at the Peter Bent Brigham Hospital.<sup>4</sup> There was evidence of influenza A infection in cases of pneumococcic pneumonia encountered here during the height of the epidemic, and the virus was isolated in cases of influenza in many other parts of the country.<sup>2</sup>

Therapy with one or more derivatives of sulfanilamide was used in all but 6 cases. In some of the cases of severe disease 9 and even 12 Gm. was given daily for several days, but in most cases the patients received the usual dose of 1 Gm. every four hours during most of the febrile stage and either 6 or 4 Gm. daily for a few days thereafter. Sulfathiazole and sulfadiazine seemed to be equally effective. Some patients were changed from one of these drugs to the other, either because the supply of sulfadiazine was temporarily exhausted or because of toxic effects

from sulfathiazole. Treatment in the cases of severe disease was continued for one to four weeks, but in cases of the milder forms the drugs were given for only two to five days. It is of particular interest that in 4 of the 6 cases of empyema (excluding the 3 cases of fulminating disease, in 2 of which the infected fluid was found at autopsy) complete recovery under chemotherapy occurred after one or more thoracenteses and did not require surgical drainage, although thick purulent fluid was obtained in some cases. The occurrence of sterile pleural effusions in cases of severe infection with recovery and the low fatality in cases with positive blood cultures are further indications of the efficacy of the drugs in the treatment of these infections.

While in 1 case of large pulmonary abscesses treatment was surgical, in others less extensive cavitation apparently healed completely without operation. Cases in which large abscesses associated with staphylococcic pneumonia healed spontaneously have been observed by one of us (M. F.) and have also been reported by Reimann.<sup>12</sup> Under such circumstances there is usually profuse purulent expectoration at the time when the fever begins to subside.

The exact role of the *Staphylococcus* in all of these cases is difficult to evaluate. The high incidence of abscesses of the lung, of empyema and of bacteremia associated with pure cultures of *Staphylococcus* is strong evidence that this organism must have played an important role in the pulmonary infections described.

Staphylococcic pneumonia has been recognized since the influenza pandemic of 1889-1890. The distinctive pathologic changes were noted by Fraenkel in cases of influenzal pneumonia and later were identified with the staphylococcic bronchopneumonias by him<sup>13</sup> and by Netter.<sup>14</sup>

In that epidemic, while the *Staphylococcus* was cultured from the lungs occasionally, it was not frequent and was not considered important. The influenza bacillus was considered by most workers to be the significant organism,<sup>15</sup> although the *Streptococcus* was thought by some, notably Finkler,<sup>16</sup> to be the important cause of the severe influenzal pneumonias.

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12. Reimann, H. A.: Primary Staphylococcic Pneumonia, *J. A. M. A.* **101**: 514-520 (Aug. 12) 1933.

13. Fraenkel, A.: *Spezielle Pathologie und Therapie der Lungenkrankheiten*, Berlin, Urban & Schwarzenberg, 1904.

14. Netter: *Etude bactériologique de la bronchopneumonie chez l'adulte et chez l'enfant*, *Arch. de méd. expér. et d'anat. path.* **4**:28-65, 1892.

15. Leichtenstern, O.: Influenza, in Nothnagel, H.: *Spezielle Pathologie und Therapie*, Vienna, Alfred Hölder, 1896, vol. 4, pt. 1, pp. 1-195.

16. Finkler, D.: Influenzapneumonie, *Deutsche med. Wchnschr.* **16**:84-86 (Jan. 30) 1890.

In the 1918 pandemic, also, while the influenza bacillus of Pfeiffer was found to be predominant in the lungs in fatal cases by many observers in some areas,<sup>17</sup> it was not frequent in others.<sup>18</sup> The hemolytic *Streptococcus* was apparently the most important organism found during that epidemic in the influenzal pneumonias that occurred in many localities, particularly in the United States Army camps.<sup>19</sup> Nevertheless, there were three reports during the 1918 epidemic of sizable groups of cases of influenzal pneumonia in which the *Staphylococcus* was the only or the predominant organism in a large proportion of the severe and fatal infections. All cases were encountered in military hospitals; the largest series, at Camp Jackson, S. C., was reported by Chickering and Park<sup>20</sup> and the others occurred at Malta<sup>21</sup> and in the Third Canadian General Hospital in France.<sup>22</sup> Since that time, individual cases or small groups

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17. (a) Report on the Pandemic of Influenza, 1918-19, Ministry of Health, Reports on Public Health and Medical Subjects, no. 4, London, His Majesty's Stationery Office, 1920. (b) Fildes, P.; Baker, S. L., and Thompson, W. R.: Provisional Notes on the Pathology of the Present Epidemic, *Lancet* **2**:697-700 (Nov. 23) 1918. (c) MacCallum, W. G.: Pathology of the Pneumonia Following Influenza, *J. A. M. A.* **72**:720-723 (March 8) 1919. (d) Hall, J. N.; Stone, M. C., and Simpson, J. C.: The Epidemic of Pneumonia Following Influenza at Camp Logan, Texas, *ibid.* **71**:1986-1987 (Dec. 14) 1918. (e) Goodpasture and Burnett.<sup>7b</sup>

18. (a) Hirsch, E. F., and McKinney, M.: Epidemic of Bronchopneumonia at Camp Grant, Illinois: Preliminary Bacteriologic Report, *J. A. M. A.* **71**:1735-1736 (Nov. 23) 1918; (b) An Epidemic of *Pneumococcus* Bronchopneumonia, *J. Infect. Dis.* **24**:594-617 (June) 1919. (c) MacCallum.<sup>17c</sup>

19. (a) Arnold, L.: Classification of *Streptococcus*: II. *Streptococci* Isolated from Influenza Throats, Classified by Sugar Fermentations, *J. Lab. & Clin. Med.* **5**:591-592 (June) 1920. (b) Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease: The Pneumonias and Other Infections of the Respiratory Tract Accompanying Influenza and Measles, St. Louis, C. V. Mosby Company, 1921. (c) Opie, E. L.; Freeman, A. W.; Blake, F. W.; Small, J. C., and Rivers, T. M.: Pneumonia Following Influenza (at Camp Pike, Ark.), *J. A. M. A.* **72**:556-565 (Feb. 22) 1919. (d) Small, A. A.: Pneumonia at a Base Hospital: Observations in One Thousand and One Hundred Cases at Camp Pike, Ark., *ibid.* **71**:700-702 (Aug. 31) 1918. (e) Miller, J. L., and Lusk, F. B.: Epidemic of *Streptococcus* Pneumonia and Empyema at Camp Dodge, Iowa, *ibid.* **71**:702-703 (Aug. 31) 1918. (f) Dwinell, W. G.: Laboratory Reports on Epidemic Pneumonia, Camp Dodge, Iowa, *Am. J. M. Sc.* **158**:216-232 (Aug.) 1919.

20. Chickering, H. T., and Park, J. H., Jr.: *Staphylococcus Aureus* Pneumonia, *J. A. M. A.* **72**:617-626 (March 1) 1919.

21. Patrick, A.: Note on *Staphylococcus Aureus* Septicemia as a Complication of Influenza in an Epidemic in Malta, *Lancet* **1**:137-138 (Jan. 25) 1919.

22. Tytler, W. H.; Janes, R. M., and Dobbin, G. M.: Pathological and Bacteriological Findings in Fatal Cases of Pneumonia During the Influenza Epidemic of October and November 1918, in *Studies of Influenza in Hospitals of the British Armies in France, 1918*, Medical Research Committee, Special Report Series. no. 36, London, His Majesty's Stationery Office, 1919, pp. 77-87.



of cases of staphylococcic pneumonia have been reported in which there was an antecedent history of influenza-like symptoms or which occurred during influenza outbreaks.<sup>23</sup> Influenza A virus was isolated, along with *Staph. aureus*, from the lungs in 3 cases of acute fulminating pneumonia during the 1936-1937 epidemic in England by Stuart-Harris and his co-workers.<sup>8</sup> They suggested that when *Staph. aureus* is the secondary invader, death is apt to occur more quickly at a time when the virus is still easy to recover. One of these cases was also reported by Scadding.<sup>9</sup> Stokes and Wolman<sup>23a</sup> also reported isolation of influenza A virus and *Staph. aureus* in a single case in 1940.

It seems clear that the *Staphylococcus* may find fertile soil in the bronchi and lungs of occasional patients with influenza. Under certain conditions this organism may assume an epidemic spread along with the causative virus of influenza. Whether such a spread requires an unusual local prevalence of the organism or some peculiarity in the pathogenicity of the strains of *Staphylococcus* is not clear. In the case of the hemolytic *Streptococcus* the experience in the United States Army camps in 1918 suggested that the preceding history of infections in any given area may play an important role in the high incidence of that organism in the influenzal pneumonias. In many of these camps the epidemic of influenza was preceded by outbreaks of scarlet fever and measles, and these, in turn, were associated with a widespread prevalence of hemolytic streptococci.<sup>24</sup> In the present instance staphylococcic pulmonary infections had been noted prior to the epidemic in more than the expected frequency and have been encountered relatively often in the ensuing months.

From a practical point of view, it would seem important to bear in mind the possibility that both staphylococci and hemolytic streptococci may be associated with severe pulmonary complications of epidemic influenza. The results of treatment with sulfathiazole and sulfadiazine in the cases reported here indicate that, except perhaps in some of the

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23. (a) Stokes, J., and Wolman, I. J.: The Probable Synergism of Human Influenza Virus and *Staphylococcus Aureus* in a Rapidly Fatal Respiratory Infection, *Internat. Clin.* **1**:115-122 (March) 1940. (b) Burgess, A. M., and Gormley, C. F.: Pneumonia in Relation to an Epidemic of "Mild" Influenza, with Report of Three Fulminating Cases Apparently Due to *Staphylococcus Aureus*, *New England J. Med.* **202**:261-264 (Feb. 6) 1930. (c) Stuart-Harris, Andrewes and Smith.<sup>8</sup> (d) Scadding.<sup>9</sup> (e) Reimann.<sup>12</sup>

24. (a) Opie, E. L.; Freeman, A. W.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Pneumonia at Camp Funston: Report to the Surgeon-General, *J. A. M. A.* **72**:108-116 (Jan. 11) 1919. (b) Clendening, L.: Reinfection with *Streptococcus Hemolyticus* in Lobar Pneumonia, Measles and Scarlet Fever and Its Prevention, *Am. J. M. Sc.* **156**:575 (Oct.) 1918. (c) Cole, R., and MacCallum, W. G.: Pneumonia at a Base Hospital, *J. A. M. A.* **70**:1146-1156 (April 20) 1918. (d) Goodpasture and Burnett.<sup>7b</sup> (e) Small.<sup>19d</sup>

severe and fulminating forms, considerable benefit may be expected from their early and intensive use. Both these drugs seemed equally effective, but sulfadiazine has proved to be considerably less toxic.<sup>25</sup> It would also seem wise, during periods of epidemic prevalence of influenza, to employ these drugs in treatment in all cases of severe influenza, particularly if cultures of sputum show that hemolytic streptococci or *Staph. aureus* are unusually prevalent in an individual patient or in a community. This procedure was adopted here and elsewhere<sup>26</sup> and may have resulted in reducing the number and severity of pulmonary complications, although that fact is difficult to establish from the available data. In cases in which the pulmonary complications have not become established, a short course of treatment lasting two or three days should suffice.

#### CONCLUSIONS

Pneumonia caused by *Staph. aureus* may occur in patients with clinical influenza and may assume epidemic proportions in local areas during an influenza epidemic. The staphylococcic infection in the lung in an individual patient may assume any of a large variety of forms, varying from simple tracheobronchitis with minimal pulmonary involvement to a fulminating acute and fatal hemorrhagic and edematous pneumonia or a chronic organizing pneumonia with bronchiectasis and multiple abscesses. Intensive treatment of such infection with sulfadiazine or sulfathiazole is indicated. A brief course of treatment with these drugs is suggested for severe uncomplicated influenza in patients who harbor large numbers of pathogenic staphylococci or hemolytic streptococci or when these organisms are known to be prevalent in a community.

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25. Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-Six Patients, *J. A. M. A.* **116**:2641-2643 (June 14) 1941.

26. (a) Menefee, E. E., Jr., and Speed, J. A.: Treatment of Infections of the Respiratory Tract with Sulfonamides, *North Carolina M. J.* **2**:611-613 (Nov.) 1941. (b) Adamson, J. D., and Flett, R. O.: The Inefficacy of Sulfapyridine in Influenza, *Canad. M. A. J.* **46**:121-123 (Feb.) 1942.

# EXOPHTHALMOS IN PATIENTS WITH VARIOUS TYPES OF GOITER

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Exophthalmos may be defined as protrusion of the globe of the eye. It occurs in diseases of the thyroid, sinusitis, intracranial arteriovenous aneurysms, benign or malignant tumors (either primary or metastatic) of the orbit or within the cranial vault, thrombosis of the cavernous sinus, myopia, xanthomatosis, congenital malformations of the skull, Paget's disease and other diseases of the bones and hypertension. It rarely appears as "voluntary" exophthalmos. The discussion in this paper will be limited to the exophthalmos that occurs in certain types of disease of the thyroid.

The mechanism of the exophthalmos associated with spontaneous or experimental thyrotoxicosis varies because of the anatomic peculiarities of different species of animals. In animals other than man stimulation of the cervical sympathetic nerves causes protrusion of the eyeball by contraction of Müller's muscle.<sup>1</sup> Although in man Müller's muscle is vestigial, many studies have been made concerning the role of cervical sympathetic stimulation in the exophthalmos of hyperthyroidism in human beings. Jonnesco<sup>2</sup> reported relief of exophthalmos in patients with toxic goiter following resection of the cervical sympathetic ganglions. Similar results were reported by Reinhard<sup>3</sup> but MacCallum and Cornell<sup>1c</sup> were unable to confirm this work. None of these investi-

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Statistical assistance was given by Dr. Nathan W. Shock, of the Department of Physiology and the Institute of Child Welfare, University of California, Berkeley.

1. (a) Müller, H., cited by MacCallum and Cornell.<sup>1c</sup> (b) Wagner, R.: Notiz über einige Versuche am Halstheile des sympathischen Nerven bei einer Enthaupteten, *Ztschr. f. rat. Med.* **5**:331-333, 1859. (c) MacCallum, W. G., and Cornell, W. B.: On the Mechanism of Enophthalmos, *Tr. A. Am. Physicians* **19**:56-63, 1904. (d) Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, *Arch. f. d. ges. Physiol.* **129**:138-144, 1909.

2. Jonnesco, T.: The Enduring Results of Total Bilateral Resection of the Cervical Sympathetic in Basedow's Disease, *Internat. Clin.* **1**:136-148, 1903.

3. Reinhard, W.: Experimentelle Untersuchungen über die Beziehungen des Halssympathicus zur Schilddrüse, *Deutsche Ztschr. f. Chir.* **180**:170-176, 1923; Die Sympathicus-Ganglion Exstirpation bei Morbus Basedowii, *ibid.* **180**:177-197, 1923.

gators checked his clinical observations by measuring the degree of exophthalmos. It remained for Unverricht,<sup>4</sup> Mutch<sup>5</sup> and Pochin<sup>6</sup> to demonstrate in precise fashion that in human beings ocular proptosis was not produced by stimulation of the cervical sympathetic nerves.

The cause of the exophthalmos frequently associated with spontaneous hyperthyroidism in human beings has been a subject of much debate and speculation. An increase in retrobulbar fat has been postulated (see the references cited by Naffziger and Jones<sup>7</sup>). Some authors have expressed the belief that venous congestion and edema were responsible for the proptosis. Daniel<sup>8</sup> suggested that in patients with hyperthyroidism excessive tone of the rectus muscles could cause formation of local tissue fluids at the rate of 2 cc. per minute per hundred grams of muscle and thus could increase the pressure in the ophthalmic veins and produce edema. In connection with this hypothesis it is interesting to note Burch's<sup>9</sup> observation that the distensibility of the skin about the eyelids is much greater than that of skin of other parts of the body. In other words, increased hydrostatic pressure may have more profound effects on the orbital tissues than on tissues elsewhere in the body.

In recent years important pathologic changes in the extraocular muscles and in other orbital tissues have been demonstrated in cases of exophthalmos. Dudgeon and Urquhart<sup>10</sup> observed degeneration and lymphocytic infiltration in the extraocular muscles of 8 of 9 patients with hyperthyroidism and noted similar changes in cardiac muscle and in the

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4. Unverricht: Experimentelle Untersuchungen über die Ursache der Exophthalmos, *Klin. Wchnschr.* **4**:878-879 (April 30) 1925.

5. Mutch, J. R.: Pupil After Cervico-Thoracic Sympathetic Ganglionectomy: Photographic Observations in Man, *Edinburgh M. J.* **43**:743-746 (Dec.) 1936.

6. Pochin, E. E.: Ocular Effects of Sympathetic Stimulation in Man, *Clin. Sc.* **4**:79-89 (June) 1939.

7. (a) Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy: Its Pathology and Treatment, *Ann. Surg.* **94**:582-586 (Oct.) 1931; (b) Progressive Exophthalmos After Thyroidectomy, *West. J. Surg.* **40**:530-543 (Oct.) 1932. (c) Naffziger, H. C., and Jones, O. W.: The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, *J. A. M. A.* **99**:638-642 (Aug. 20) 1932. (d) Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, *Arch. Ophth.* **9**:1-11 (Jan.) 1933; (e) Progressive Exophthalmos Associated with Disorders of the Thyroid Gland, *Ann. Surg.* **108**:529-544 (Oct.) 1938.

8. Daniel, R.: Enophthalmos Associated with Hyperthyroidism: Suggestion Regarding Other Possible Factors in Etiology, *Proc. Staff Meet., Mayo Clin.* **13**:683-688 (Oct. 26) 1938.

9. Burch, G. E.: Formation of Edema in Eyelids of Man: Influence of Local Tissue Pressure, Skin Distensibility, Lymph Flow, Intraorbital Pressure Gradient and Venous Pressure, *Arch. Int. Med.* **65**:477-498 (March) 1940.

10. Dudgeon, L. S., and Urquhart, A. L.: Lymphorrhages in Muscles in Exophthalmic Goiter, *Brain* **49**:182-186 (June) 1926.

deltoid, rectus femoris and biceps muscles. Von Zalka <sup>11</sup> found an increase in size and lymphocytic infiltration in the extraocular muscles of 16 patients who died of exophthalmic goiter. These changes, which also have been described by other observers, are similar to those noted by Naffziger and Jones <sup>7</sup> in patients with progressive exophthalmos, "round cell infiltration, marked edema, destruction of muscle fibers and complete loss of architecture with an increase in fibroblasts and a generalized fibrosis."<sup>7a</sup> Smelser <sup>12</sup> has stressed edema and abnormalities of tissues other than muscle in the orbit of animals—a point not emphasized in studies reported on human beings. These mechanical changes are sufficient to account for the exophthalmos in patients with spontaneous thyrotoxicosis. The primary mechanism behind these pathologic changes in the orbit is not clear, but recent work would indicate that it is related to the function

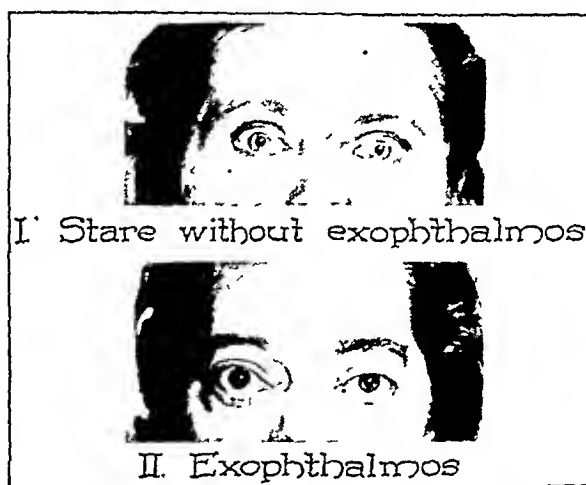


Fig. 1.—The eyes of the patient in the upper photograph measure 15 mm. from the deepest part of the lateral wall of the orbit to the point of greatest convexity of the cornea, while those of the patient in the lower photograph measure 25 mm. (left eye) and 27 mm. (right eye).

of the anterior lobe of the pituitary and perhaps of the gonads and the adrenal cortex.

One of the reasons for confusion as to the presence or absence of exophthalmos has been the failure of many clinicians to distinguish "stare," or retraction of the upper (and perhaps the lower) lid, from protrusion of the eyeball (fig. 1). The statement one hears so fre-

11. von Zalka, E.: Ueber die Veränderungen der äusseren Augenmuskeln und ihre Bedeutung bei Morbus Basedowii, *Beitr. z. path. Anat. u. z. allg. Path.* **92**:239-252, 1933.

12. Smelser, G. K.: The Histology of Orbital and Other Fat Tissue Deposits in Animals with Experimentally Produced Exophthalmos, *Am. J. Path.* **15**:341-352 (May) 1939; The Role of the Cervical Sympathetic Ganglia and Müller's Orbital Muscle in Experimental Exophthalmos, *Am. J. Ophth.* **22**:1201-1209 (Nov.) 1939.

quently that "the eyes snapped back after the goiter was removed" usually means that the stare disappeared; it usually does not mean that the eyeball protruded to a lesser degree. Clinical impressions of the degree of prominence of the eyes may be misleading in enophthalmos as well as in exophthalmos. For example, it has been assumed generally that enophthalmos occurs in Horner's syndrome (paralysis of the cervical sympathetic nerves) in human beings; yet Wagener<sup>13</sup> and Pochin<sup>6</sup> showed by measurement with an exophthalmometer that enophthalmos was not present consistently. This observation is confirmed in the present report. Ptosis of the upper lid and elevation of the lower lid give an illusion of enophthalmos that is readily dispelled when the eyes are observed with the lids gently closed.

Several other clinical situations may give rise to a false impression of exophthalmos. Lid lag is not infrequently associated with unilateral ptosis of an upper eyelid. The ptosis is compensated partially by elevation of the upper eyelid and the eyebrow through contraction of the frontalis muscle. This condition, associated with overaction of the contralateral levator palpebrae superioris, caused lid lag in the opposite eye. Lid lag may be seen in normal persons or in anxious patients who show evidences of sympathetic overactivity. Realization of these factors would prevent acceptance of these false clues as evidences of hyperthyroidism.

There are a number of simple clinical correlations that aid in estimating exophthalmos. The distance from the deepest portion of the lateral wall of the orbit to the point of greatest convexity of the cornea may be determined and compared with similar observations on normal persons. In persons with exophthalmos the eyes have a staring and uncomfortably prominent appearance. Palpation with the fingers gives a sensation of increased orbital resistance. Lacrimation is excessive and may be associated with conjunctival injection and subjective discomfort. Periorbital edema is common. Patients often complain of a sense of pressure behind the eyes. Edema of the sclera, although infrequent in ordinary degrees of exophthalmos, is common in patients with severe progressive exophthalmos. Due to greater lid retraction on one side, more sclera may show in one eye than in the other, but usually measurement reveals little difference in the prominence of the two eyes, although differences of 1 to 4 mm. have been noted. Impaired convergence is nearly always present in patients with exophthalmos and may be found in the absence of exophthalmos. Diplopia is rare unless exophthalmos really exists. Lid lag may be present without exophthalmos.

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13. Wagener, H. P.: Enophthalmos in Horner's Syndrome, *Tr. Am. Ophth Soc.* **31**:166-175, 1933.

The foregoing discussion shows that the presence of exophthalmos can be confirmed only by careful observation and by actual measurement. The instrument used in the studies reported here was the Hertel exophthalmometer<sup>14</sup> (figs. 2 and 3). The instrument allows the observer to measure the distance between the deepest part of the lateral wall of the bony orbit (situated at or just below the frontozygomatic junction) and the point of greatest convexity of the cornea. The two

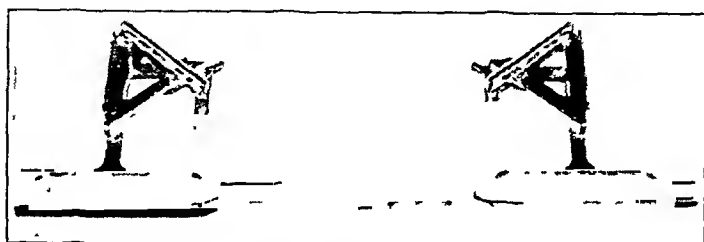


Fig. 2.—The Hertel exophthalmometer.



Fig. 3.—Manner of using the Hertel exophthalmometer. The arrow points to the reflection of the cornea.

eye pieces are so arranged that the distance between them may be varied according to the variable distances between individual pairs of eyes. Once the optimum position for placing of the eye pieces is found, the distance, which is recorded in millimeters (as "Bar at 105"), is used for all subsequent measurements on the same patient. The distance in each eye from the greatest depth of the lateral orbital wall to the anterior part of the cornea also is recorded in millimeters. The patient is seated

14. Hertel: Ein einfaches Exophthalmometer, *Arch. f. Ophth.* 60:171-174, 1905

upright with his eyes directed straight ahead while the readings are made. These measurements are made with the aid of two mirrors set at right angles (figs. 2 and 3).

The purpose of this paper is to record the measurements of the eyes of (1) 65 normal persons, (2) 106 patients with toxic diffuse goiter, (3) 52 patients with toxic nodular goiter, (4) 55 patients with nontoxic nodular goiter and (5) 2 patients before and after unilateral paralysis of the cervical sympathetic ganglions.

#### NORMAL PERSONS

Only a few measurements of the eyes of normal persons have been reported in the literature. The measurements on 200 normal persons published in "The American Encyclopedia and Dictionary of Ophthalmology"<sup>15</sup> averaged 12 to 14 mm. Ruedemann<sup>16</sup> obtained readings of 14 to 20 mm. on 1,000 normal persons. Wagener<sup>13</sup> found that in 80 per cent of 200 persons the measurements fell between 15 and 20 mm., with a range of 11 to 24 mm. Brain<sup>17</sup> obtained an average reading of 12.5 mm. but did not state the number of subjects examined; he later reported a maximum reading of 16 mm. (with the Hertel instrument).

My own measurements were made on 65 normal persons. The mean age was 32 years. The group consisted of 42 women (mean age 32 years) and 23 men (mean age 31.9 years). The youngest person was 19 and the oldest 51. The mean distance for each eye was 15.9 mm., and the range was 11.5 to 20 mm. (table 1).

The range of measurement in normal persons is wide. Great variations are observed in the prominence of the eyes as well as in the shape of the nose. One eye may be more prominent than the other. In addition, the inevitable error in measurement, as determined by repetition, is usually about 0.5 mm. but may be 1 mm. or more (von Birch-Hirschfeld,<sup>18</sup> Pochin<sup>6</sup>). If different observers measure the eyes of the same person, even with the same instrument, the error obviously is even

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15. Wood, C. A.: The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1915, vol. 7, p. 4851.

16. Ruedemann, A. D.: The Ductless Glands as They Appertain to Eye Diseases and to Surgery, J. A. M. A. **97**:1700-1704 (Dec. 5) 1931; Exophthalmos, Cleveland Clin. Quart. **4**:66-75 (Jan.) 1937; Eye Changes Accompanying Hyperthyroidism, Ohio State M. J. **26**:318-320 (April) 1930.

17. Brain, W. R.: Exophthalmic Ophthalmoplegia, Tr. Ophth. Soc. U. Kingdom **57**:107-115, 1937. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, with Pathological Report on Ocular Muscles and Thyroid Glands, Quart. J. Med. **7**:293-323 (April) 1938.

18. von Birch-Hirschfeld: Ein neuer Exophthalmometer, Klin. Monatsbl. f. Augenh. **38**:721-726, 1900.



greater. The error is minimized by practice on the part of the operator and by careful placing of the instrument for each measurement. All the readings recorded in this study were made over a period of about five and a half years by the same observer with the same instrument.

#### PATIENTS WITH TOXIC DIFFUSE GOITER

This group consisted of 106 patients, all of whom had unquestioned hyperthyroidism, as determined by carefully taken histories, physical examinations and pertinent laboratory tests. All the patients whose thyroids contained nodules were eliminated from this group. The thyroids from all the patients, with the exception of those who were treated with roentgen rays, were examined pathologically.<sup>19</sup> The glands

TABLE 1.—*Eye Measurements* \*

Subjects	Eye †	Number of Subjects	Mean	Standard Deviation of Distribution	$\sigma$ Mean	Range
Normal persons	OD	65	15.9	1.84	0.23	11.5-20.0
	OS	65	15.9	1.75	0.22	
Patients with nontoxic nodular goiter	OD	55	15.8	1.92	0.26	12.5-20.5
	OS	55	15.8	1.90	0.26	
Patients with toxic diffuse goiter	OD	106	17.7	2.70	0.26	11.0-23.0
	OS	106	17.6	2.56	0.25	
Patients with toxic nodular goiter	OD	52	16.6	2.90	0.40	11.0-22.5
	OS	52	16.5	2.74	0.38	

\* All measurements were made in millimeters.

† The following abbreviations have been used: OD, right eye; OS, left eye.

were cut serially, and representative sections were examined microscopically. Twenty-five of these patients were men (mean age 39.4 years), and the remainder were women (mean age 33.9 years). The mean age of the group was 35.2 years; the youngest patient was 12 years of age and the oldest 60. The mean measurement was 17.7 mm. for the right, and 17.6 mm. for the left, eye. The results of the statistical study are shown in table 1. All measurements were made before surgical or roentgen treatment had been instituted.

As in normal persons, the prominence of the eyes in patients with toxic diffuse goiter varies widely. But a sufficient number of these patients had more prominent eyes than normal persons so that the probability of the mean difference of approximately 1.8 mm. being a chance

19. A clinicopathologic study of disease of the thyroid in over 500 patients followed up for as much as six years after treatment is being carried out with Dr. Karl B. Eichorn. The patients referred to in the study reported here are included in the larger group of 500 patients.

phenomenon is less than 1 in 100,000 (table 2). In other words, these measurements confirm the presence of exophthalmos in patients with "exophthalmic" goiter. Of the group of 106 patients studied here, 71 had clinical exophthalmos. In these, the average measurement of the right eye was 18.6 mm., and that of the left, 18.5 mm. Thus, in patients with clinical exophthalmos the eyes are more prominent by measurement than in patients without clinical exophthalmos.

It is interesting to compare the results of a relatively precise method of estimating exophthalmos with clinical impressions. In this series of 106 patients 33 per cent had more prominent eyes than all but 5 per cent. of the normal persons. In Cattell's series of 800 patients with exophthalmic goiter<sup>20</sup> 364, or 46 per cent, had exophthalmos as determined by the clinician's impression.

TABLE 2.—*Significance of Differences in Eye Measurements\* of Patients with Various Types of Goiter*

Type of Goiter	Right Eye			Left Eye		
	Mean Difference	$\sigma$ Difference	Critical Ratio †	Mean Difference	Difference	Critical Ratio
Nontoxic nodular and normal condition .....	-0.11	0.35	-0.31	-0.03	0.34	-0.09
Toxic diffuse goiter and normal condition .....	1.78	0.35	5.09	1.75	0.33	5.30
Toxic nodular goiter and normal condition .....	0.67	0.46	1.46	0.66	0.44	1.50
Toxic diffuse goiter and toxic nodular goiter .....	-1.11	0.48	-2.31	-1.09	0.45	-2.42

\* All measurements were made in millimeters.

† A critical ratio of 5.0 means roughly that the probabilities of the difference being a chance phenomenon are about 1 in 100,000.

Seventy-eight of the 106 patients were followed up for five years or longer. Of these, 59 were treated by subtotal thyroidectomy (surgical), 16 by roentgen therapy and 3 both by surgical intervention and by roentgen therapy (of these 3, 2 had surgical treatment first and 1 had roentgen treatment first). In 38 of these 78 patients the increase in the prominence of one or both eyes was 1.5 mm. or more in an average of ten and eight-tenths months after treatment; in 19 the increase was 0.5 to 1.0 mm.; in 9 no change occurred; in 6 a decrease of 0.5 to 1.0 mm. was noted, and in 6 the decrease was 1.5 mm. or more. Of the 38 patients whose eyes became significantly more prominent, 13 had either hypothyroidism or frank myxedema. The average weight of the thyroids removed from patients whose eyes became more prominent was 2 Gm. greater than that of the glands of patients whose eyes did not become

20. Cattell, R. B.: Eye Complications in Exophthalmic Goiter: Cataracts and Exophthalmos, *Ann. Surg.* 100:284-303 (Aug.) 1934.

more prominent. The changes in body weight were as follows: Those patients with a significant increase in exophthalmos gained an average of 21.5 lb. (10 Kg.); those with no change in the eyes gained an average of 18.5 lb. (8 Kg.), and those whose eyes regressed significantly gained an average of 15.6 lb. (7 Kg.). Only 3 of the 16 patients treated with roentgen rays alone had an increase of 1.5 mm. or more in one or both eyes, in contrast to 34 of 59 patients treated surgically.

The only apparent explanation for the relatively greater incidence of what may be termed mildly progressive exophthalmos in the surgically treated patients is that in general their thyroid function changes much more rapidly from a state of hyperactivity to a normal or subnormal state. On the other hand, when roentgen therapy is used, recovery is a much slower process in which even relatively rapid changes seldom are seen. Hypothyroidism did not develop in any of the patients so treated.

At the 1941 meeting of the Association of American Physicians Dr. James H. Means stated that in patients with exophthalmic goiter in whom the exophthalmos was one of the prominent symptoms the treatment should be directed toward relieving the ocular condition. He suggested that radical subtotal thyroidectomy probably should be avoided. The results reported here (presented at the 1941 meeting of the Association for the Study of Internal Secretions) bear out his contention. They certainly do not support the opinion of many surgeons that patients with severe exophthalmos should have their thyroids removed surgically rather than treated by roentgen ray "in order to prevent the progress of exophthalmos."

#### PATIENTS WITH TOXIC NODULAR GOITER

Since these patients fall in the group which has aroused the most discussion among physicians interested in hyperthyroidism, it is well to begin with a definition of terms. Simply stated, all 52 patients had unquestioned hyperthyroidism as well as nodular thyroids. One patient only was not operated on; she was included because all members of the Thyroid Committee at the University of California Hospital agreed on the diagnosis of toxic nodular goiter. The thyroids from all the other patients were sectioned serially; macroscopic nodules were noted, and representative sections were cut and studied microscopically. As to the definition of a nodule, it is considered to be a localized area of thyroid tissue completely surrounded by a connective tissue capsule. Most of the thyroids from these patients contained one or more nodules that were recognized grossly with ease. Most of the thyroids also showed hyperplasia within the nodules, in the rest of the gland or in both areas. One thyroid consisted of a large, hyperplastic nodule which comprised over

90 per cent of the total amount of thyroid tissue present; no signs of hyperplasia were noted in the remaining tissue.

The mean measurements of the eyes in this group were 16.6 mm. for the left eye and 16.5 mm. for the right one. Thus, the eyes of patients with toxic nodular goiter are more prominent than those of normal persons. But this difference is of only borderline significance, since it could occur by chance thirty times out of a hundred.

Twenty-seven of these patients, 25 women and 2 men, were followed up as much as fifty-four months. The mean age was 44.7 years; the 2 men were 37 and 54 years of age, respectively. Table 1 gives the statistical analysis. Eight patients' eyes became 1.5 mm. more prominent in an average of eleven and a half months after subtotal thyroidectomy; 11 patients' eyes became 0.5 to 1.0 mm. more prominent in an average of four and a half months; the eyes of 6 showed no change, and the eyes of only 2 showed a decrease of 1.5 mm. or more in an average of thirty-eight months after treatment.

On the whole, the patients in this group apparently had less exophthalmos than those with toxic diffuse goiter. Many explanations have been offered for this difference. Marine<sup>21</sup> expressed the opinion that the gonads must be active in order to produce experimental exophthalmos in rabbits. If gonadal activity becomes important in the human being, the older age of the patients might explain the lesser tendency to have exophthalmos. As stated, the average age of patients in this group was 44.7 years (range, 17 to 70), and, all but 2 being women, many of them were past the menopause. However, this explanation is not impressive when one sees from a review of the data that of the 8 patients (all women) whose eyes became significantly more prominent after operation, the youngest was 24 and the others were 42, 46, 49, 50, 55, 60 and 70 years of age, respectively. In general, if persons with hyperthyroidism have nodular goiter, the disease is of considerable duration and probably not severe, as evidenced by the failure of these patients to seek medical care early. The longer and milder course may allow for compensatory adjustments which prevent extensive orbital changes that might result in severe degrees of exophthalmos. It is apparent that these data permit no final answer. Indeed, one can only speculate on it on the basis of the results noted.

#### PATIENTS WITH NONTOXIC NODULAR GOITER

This group comprised 55 patients, all of whom had had subtotal or partial thyroidectomy and showed no signs or laboratory evidence of hyperthyroidism. The thyroids were studied pathologically as described

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21. Marine, D.: Pathology and Physiology of Exophthalmos, *Ann. Int. Med.* 12:443-453 (Oct.) 1938.

in the section on toxic nodular goiter, and all were found to contain encapsulated nodules by macroscopic and microscopic examination. Forty-nine of these patients were women whose average age was 42.32 years (range, 10 to 68), and 6 were men whose average age was 41.66 years (range, 26 to 64). The average age for the group was 42.25 years. Table 1 shows the number of patients, the mean measurements of the eyes, the standard deviation of this mean and the range. The conclusion was that the eyes of patients with nontoxic nodular goiter are no more prominent than those of normal persons.

Twenty-three of these patients were followed up for as long as thirty-five months after operation. In 3 the increase in the prominence of the eyes was 1.5 mm. or more in an average of nine and six-tenths months after operation (range, two and three-tenths to nineteen months); in 10 the increase was 0.5 to 1.0 mm.; in 2 no change occurred;

TABLE 3.—*Measurements of Eyes Before and After Unilateral Paralysis of the Cervical Sympathetic Ganglions*

Time	Position of Eye Pieces in Ophthalmometer	Right Eye, Mm.	Left Eye, Mm.
Before injection of right stellate ganglion.....	Bar at 107	18.5	17.0
20 minutes after.....	Bar at 107	18.5	16.5
40 minutes after.....	Bar at 107	18.0	16.5
Before injection of right stellate ganglion.....	Bar at 103	17.5	16.5
25 minutes after.....	Bar at 103	17.5	16.5

in 7 a decrease of 0.5 to 1.0 mm. was noted, and in 1 a decrease of 1.5 mm. occurred.

There is no apparent explanation for the increase in the protrusion of the eyes (significant or otherwise) in these patients. It was not due to gain in weight, for many of these patients showed no significant increase in weight. Indeed, many of them also were put on reducing diets (adequate in protein, minerals and vitamins), and lost weight as part of the general program of treatment.

#### PATIENTS WITH UNILATERAL PARALYSIS OF THE CERVICAL SYMPATHETIC GANGLIONS

In order to measure any possible change in the prominence of the eyes following paralysis of the cervical sympathetic ganglions measurements were made before and after unilateral injection of procaine hydrochloride into the cervical sympathetic ganglions of 2 patients; 1 was a 39 year old man with rheumatic heart disease, a nontoxic goiter and pulmonary embolism, and the other was a 56 year old woman who had hypertensive heart disease and pulmonary embolism. Table 3 gives the results of this study.

At the time when the eyes of both patients were measured after injection into the stellate ganglion, a clearcut Horner's syndrome was evidenced clinically by miosis, ptosis of the lid, conjunctival injection and increased warmth of the arm on the side of the body on which the injection was done (the right in each case). According to the unbiased opinion of 2 observers, the eye on the affected side appeared enophthalmic in each case; but this was not borne out by the measurements. I previously had measured the eyes of several patients who had Horner's syndrome from tumors that caused paralysis of the cervical sympathetic ganglions and had been struck by the fact that the enophthalmos was apparent rather than real. In these patients the eyes had not been measured before Horner's syndrome had manifested itself. The results of the measurements both before and after paralysis of the cervical sympathetic nerves agree with the data reported by Pochin<sup>6</sup> and Wagener.<sup>13</sup>

#### COMMENT

Stare and exophthalmos are two different manifestations that may occur as part of the syndrome associated with hyperthyroidism. The most likely cause of exophthalmos is a change and increase in the size of the extraocular muscles and the tissues of the orbit which, situated in an area enclosed on all but one side, cause proptosis of the eyeball. Progressive exophthalmos is the most extreme result of these pathologic changes which are found to some degree in the majority of patients suffering from hyperthyroidism. It would seem from these studies that in most thyrotoxic patients treatment of the hyperthyroidism itself does not cause sufficient regression of the pathologic processes in the orbital tissues to result in a regression of the exophthalmos. In fact, the majority of these patients have what might be termed a mildly progressive exophthalmos which can be determined better by actual measurement of the prominence of the eyes than by clinical observations. Nevertheless, many clinicians even without recourse to measurements have felt that the exophthalmos did not improve. In some patients the eyes may become more prominent after treatment and then regress to a certain degree. A decrease only in the measurable exophthalmos following subtotal thyroidectomy occurs in less than 10 per cent of the thyrotoxic patients. Recently Grace and Weeks<sup>22</sup> reported no change in exophthalmos following subtotal thyroidectomy in 80 patients with toxic goiter.

The eyes of some normal persons are as prominent as those of patients with hyperthyroidism but usually do not show abnormalities of the orbital tissues, stare or lid lag. Unlike the eyes of thyrotoxic

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22. Grace, R. V., and Weeks, C.: Surgery of the Thyroid in a Large Municipal Hospital, *Ann. Surg.* **113**:496-507 (April) 1941.

patients with exophthalmos, which give the impression of being pushed forward, the eyes of normal persons may be described as not uncomfortably prominent. However, the borderline between normal and abnormal may be as difficult to determine by measurement as by less precise clinical observations. This is illustrated in figure 4. It is apparent that the exophthalmometer is only an aid in the study of exophthalmos. If measurements of eyes of patients with exophthalmic goiter can dispel false clinical impressions, they may pave the way to further investigative work that will allow a more satisfactory solution to this problem.

#### SUMMARY

No reports have appeared in the literature concerning the changes that occur in the eyes of patients with various types of thyroid disease which have been measured before and after treatment with the aid of an exophthalmometer. According to the studies reported here, the eyes

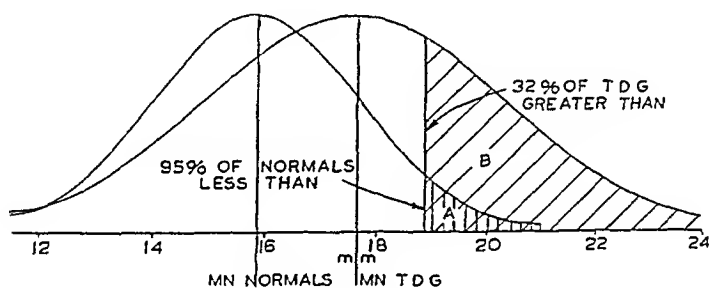


Fig. 4.—Distribution curves for eye measurements in normal persons and in patients with toxic diffuse goiter (T. D. G.). The more coarsely shaded area indicates the percentage of patients with toxic diffuse goiter whose eyes were more prominent than those of all but 5 per cent of the normal persons. The figures on the abscissa give the measurements in millimeters from the deepest point of the lateral wall of the orbit to the point of greatest convexity of the cornea.

of patients with nontoxic nodular goiter are no more prominent than those of normal persons. Patients with toxic nodular goiter tend to have more prominent eyes than normal persons but not as prominent as patients with toxic diffuse goiter. The eyes of patients with toxic diffuse goiter are significantly more prominent than those of normal persons or of patients with nontoxic nodular goiter.

The eyes of over 50 per cent of the patients with toxic diffuse goiter become measurably more prominent after subtotal thyroidectomy; they become less prominent in only a small percentage of persons. These observations are contrary to the opinion of most surgeons who have relied on clinical impressions as to the state of exophthalmos before and after treatment. It is apparent that loss of the stare associated with hyperthyroidism does not necessarily mean a decrease in exophthalmos.



Fig. 5.—Photomicrograph of a section of thyroid from a patient with nodular goiter and hyperthyroidism of long duration.



Fig. 6.—Photomicrograph of a section of thyroid from a patient with nontoxic nodular goiter of many years' duration.



The eyes of thyrotoxic patients treated by roentgen rays show less tendency to increase in prominence. It is suggested, therefore, that for patients with hyperthyroidism in whom exophthalmos is severe, roentgen therapy is more desirable than surgical subtotal thyroidectomy. Furthermore, as also intimated by Dr. James H. Means, it is advised that the treatment in this particular group be directed toward preventing the occurrence of malignant exophthalmos.

NOTE.—Since this paper was submitted for publication Aird<sup>23</sup> and Hertz, Means and Williams<sup>24</sup> have made pertinent reports.

University of California Hospital.

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23. Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Hormone, *Ann. Int. Med.* **15**:564-581 (Sept.) 1941.

24. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, *West. J. Surg.* **49**:493-498 (Sept.) 1941.

# UNUSUALLY HIGH INSULIN REQUIREMENTS IN DIABETES MELLITUS

REPORT OF A CASE

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There is no definite dextrose-insulin ratio applicable to all persons with diabetes. The amount of insulin needed to control the defective carbohydrate metabolism of any one patient must be determined empirically and may vary from time to time. Although diabetic persons with large insulin requirements are encountered infrequently, a number of cases of such requirement have been reported since the introduction of the hormone in 1922. These cases may be divided into two groups. In one the large insulin requirement is associated with some recognizable complication, such as diabetic ketosis, an infection, an endocrine disorder, hepatic disease or some other intercurrent illness. In the second there is no definite cause to account for the large amount of insulin that must be administered. This group, though small, includes some of the most extreme examples of huge insulin need.<sup>1</sup> Clinical and postmortem studies in such cases have revealed little to explain the pathogenesis of the insulin-resistant state. This report deals with a case of diabetes mellitus with a large insulin requirement, the cause of which could not be determined. A review of the literature revealed only 1 other case<sup>1b</sup> in which the maximum twenty-four hour dose (3,250 units) exceeded the greatest amount (2,795 units) administered to this patient. Of unusual interest was the complete disappearance of the excessive need for insulin six months after its sudden onset.

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From the Second Medical Service and the Diabetic Clinic, Mount Sinai Hospital.

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## REPORT OF CASE

A 60 year old Polish-born married Jewess was admitted to Mount Sinai Hospital on Jan. 22, 1940 for control of diabetic ketotic acidosis. She had 6 children living and well. She stated there was no family history of diabetes. Her past history was not remarkable except for an appendectomy in 1926.

In 1930, ten years before admission, glycosuria had first been discovered. Dietary restrictions alone had served to control the glycosuria for the next seven years. In 1937 she had had an attack of pneumonia, which precipitated a diabetic ketotic coma. Since that time she had required 10 units of protamine zinc insulin once daily. About one month before admission, polyuria, polydipsia and persistent glycosuria had developed. Her insulin dosage was gradually increased to 40 units daily. She lost weight and complained of headaches and generalized aches and pains. At times she seemed slightly irrational. After several days of nausea and increasing drowsiness, she presented herself for admission to the hospital.

On physical examination at the time of admission the patient was thin, flushed and drowsy. She was fully conscious, however, and responded well to questions. The tension of the eyeballs seemed normal. Ophthalmoscopic examination revealed hard white exudates typical of a diabetic retinopathy in each macular region. The heart was slightly enlarged to the left. There was a soft systolic murmur over the entire precordium, best heard over the base. The blood pressure was 200 systolic and 100 diastolic, measured in millimeters of mercury. No abnormalities of the lungs were noted. The abdomen was scaphoid, and the liver was not palpable. Both calves were tender on pressure. There were varicosities on each leg, with an area of eczema on the lateral aspect of the lower part of the left leg. There was no edema. A neurologic examination revealed depressed knee and ankle jerk reflexes in both legs and mild weakness of the extensors of the feet and the adductors of the thighs.

On admission the urine gave a positive reaction (4 plus) for reducing sugars with Benedict's reagent. The sodium nitroprusside test for acetone yielded a positive reaction (3 plus). The heat and acetic acid test for albumin gave a 3 plus reaction. Microscopic examination disclosed many clumps of white cells and occasional red cells and granular casts. The hemoglobin concentration was 75 per cent (Sahli 14.5 Gm. standard). The white cell count was 6,600 per cubic millimeter. A differential count of the stained smear showed 36 per cent polymorphonuclears, 57 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. The sedimentation time for 18 mm. (Linzenmeier) was thirty minutes. The Wassermann complement fixation reaction was negative. The blood per hundred cubic centimeters contained 455 mg. of sugar, 10 mg. of urea nitrogen and 415 mg. of total cholesterol. The carbon dioxide content was 37.5 volumes per cent.

The clinical impression was moderate diabetic ketotic acidosis, diabetic retinopathy, peripheral neuropathy, essential hypertension and generalized arteriosclerosis.

*Course and Treatment.*—The patient was given fluids by mouth and 120 units of unmodified insulin in divided doses in twenty-four hours. At the end of this period the urine was free of sugar but still contained a trace of acetone occasionally. Although she complained of abdominal cramps and had frequent stools, her general condition was considered good. She took fluids well and was served a full diabetic diet of 150 Gm. of carbohydrate, 80 Gm. of protein and 60 Gm. of fat. During the next forty-eight hours (January 24 and 25) she had no acetonuria and slight glycosuria on 40 units of regular insulin daily.

On the fourth day of hospitalization (January 26) mild ketonuria and moderate glycosuria occurred despite 55 units of insulin. On the fifth day (January 27)

the content of sugar in blood drawn while the patient was fasting was 455 mg. per hundred cubic centimeters. She was again given 55 units of insulin, with the persistence of glycosuria (3 to 4 plus) and slight acetoneuria in the late evening hours. On the sixth day (January 28) she was given 30 units of protamine zinc insulin before breakfast. Toward evening a large amount of acetone was found in the urine, and 60 additional units of regular insulin was given as well as an infusion of 1,750 cc. of 5 per cent dextrose in physiologic solution of sodium chloride.

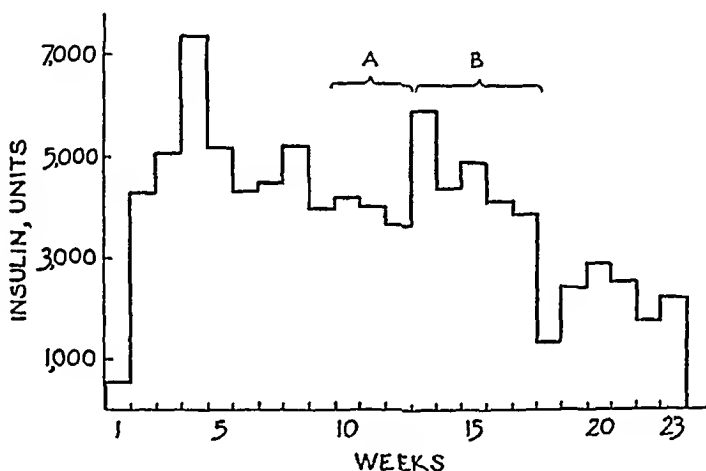
TABLE 1.—*Insulin Dosage, Fluid Balance and Degrees of Glycosuria and Acetoneuria on the Ninth and Tenth Days of Hospitalization of a Diabetic Patient with a Large Insulin Requirement*

Time	Insulin Dose, Units*	Intra- venous Fluid Intake, Cc.	Urine Output, Cc.	Glycosuria		Aceto- nuria	Comment
January 31							
6:00 a.m.	50 (protamine zinc insulin)	200	300	4+		4+	Irrational
7:00	30	300	...	4+		4+	
10:30	20	500	300	4+		4+	Incontinent of urine
2:00 p.m.	..	400	300	4+		4+	
3:00	30	...	400	4+		4+	
4:00	50	...	350	4+		4+	Infusion band torn off by patient
5:00	100	..	530	4+		4+	
				%	Gm.		
6:00	30	...	500	2.9	15	4+	Response to name
7:00	50	400	400	3.1	12	4+	Physiologic solution of so- dium ehloride given intra- venously in place of 5% dextrose in saline solution or lactate-Ringer's solution
7:30	100						
8:00	100	250	300	3.0	9	4+	
9:00	200	275	320	3.0	9.6	4+	Patient responding better
10:30	200	275	300	3.0	9	4+	
11:30	200	...	200	2.9	6	4+	Some fluid taken by mouth
February 1							
12:30 a.m.	200	300	200	2.9	6	4+	
1:30	200 (i.v.)	300	150	2.5	3.8	4+	No change
2:30	200 (i.v.)	300	120	2.3	2.7	4+	Still confused
3:30	200	300	100	1.8	1.8	4+	
4:30	200	600	100	1.0	1.0	3+	Talk more rational
5:30	200	800	100	0.6	0.6	2+	
6:30	...	600	220	0	0	Trace	5% dextrose in physiologic solution of sodium ehloride given intravenously
7:30	100 (protamine zinc insulin)	200	160	0	0	Trace	Considerable fluid taken by mouth
8:30	50	...	170	0	0	0	

\* Unless otherwise specified regular insulin was administered.

On the seventh day (January 29) the ketonuria continued unabated. The patient complained of weakness and drowsiness and appeared dehydrated. She was given 30 units of protamine zinc insulin, 120 units of regular insulin and a continuous infusion of 3,950 cc. of 5 per cent dextrose in saline solution alternating with lactate-Ringer's solution, but the ketonuria did not subside. On the eighth day (January 30) the insulin was increased to 50 units of protamine zinc insulin and 180 units of regular insulin, without noticeable benefit. The intravenous fluid intake remained at 3,000 cc. During the subsequent twenty-four hours she became stuporous. Analysis of the blood on the morning of the ninth day (January 31) showed a sugar content of 300 mg. per hundred cubic centimeters and a carbon dioxide content of 27 volumes per cent. During the first twelve hours of the ninth

day she was given a total of 310 units of insulin (table 1). A total of 1,400 cc. of 5 per cent dextrose in saline solution and lactate-Ringer's solution was given intravenously. The degree of ketonuria (4 plus) was unaffected, and the patient's fluid balance remained negative. Because of the refractory ketosis insulin was increased rapidly to 200 units per hour, and 2,000 units was given in a ten hour period. Two 200 unit doses were given intravenously. At the same time the intravenous fluid was changed to physiologic solution of sodium chloride, and 4,600 cc. was given in twelve hours. Throughout the entire period the patient could be aroused, and at times she took small amounts of fruit juice by mouth. Her blood pressure varied between 128 and 160 systolic and remained at 70 diastolic, measured in millimeters of mercury. She gradually became less stuporous, and her urine showed less sugar and acetone (2 plus). Finally, sugar and acetone disappeared from the urine, and there was a striking fall in the urine output, indicating an increased ability to retain fluid. During the last twenty-four hours of this ketotic episode the patient received 2,360 units of insulin and 6,000 cc. of fluid by vein. On the eleventh day (February 2) her urine was free of sugar



The weekly total doses of insulin administered during hospitalization. *A*, the period of roentgen irradiation over the pituitary (March 26 to April 17). *B*, the period of lipocaic therapy (April 21 to May 24).

and acetone until the late afternoon after a dose of 100 units of protamine zinc insulin. With the reappearance of dextrose and a faint trace of acetone in the urine 450 units of unmodified insulin was given in divided doses until the urine cleared. On the twelfth day (February 3) the sugar content of blood drawn while the patient was fasting was 70 mg. per hundred cubic centimeters, the blood content of carbon dioxide was 47.1 volumes per cent and a single dose of 100 units of protamine zinc insulin before breakfast kept the urine free of dextrose and acetone.

The subsequent course was characterized by the continuation of the need for large doses of insulin (figure). The daily dose fluctuated, and a plateau of 1,000 units of protamine zinc insulin and regular insulin a day was reached during the fourth week of hospitalization. As much as 2,500 units of insulin during a single day (February 22) was necessary to eliminate ketonuria during the fifth week. On a number of occasions mild symptoms of hypoglycemia developed, but the patient responded promptly to oral or parenteral administration of dextrose. Two hundred units of insulin added to or subtracted from the total daily dose had

little demonstrable effect on the course of the diabetes. On one occasion a 300 unit dose of protamine zinc insulin was doubled by mistake. Despite the 600 unit initial dose, no reduction of subsequent doses of insulin was necessary.

The patient maintained an average weekly requirement of 4,200 units of insulin during the first fifteen weeks in the hospital. The average daily dose of insulin was 700 units during the first month, 593 units in the second, 615 units in the third, 446 units in the fourth and 324 units in the fifth and last month. The total amount of insulin administered was 85,680 units.

Two weeks after admission hepatomegaly was noted, and it persisted until discharge five months later. A smooth, nontender edge of the liver could be felt 2 fingerbreadths below the costal margin. The results of hepatic function tests, described in the next section of the case report, showed no deviation from normal.

On April 16, about three months after admission, the patient's temperature rose to 101 F. and watery diarrhea developed. Several other patients in the same ward were afflicted simultaneously. After repeated culture of fecal material, *Bacillus dysenteriae* Flexner was isolated from this patient and some of the others. Agglutination tests for typhoid, paratyphoid and dysentery organisms gave negative results. The diarrhea subsided on symptomatic therapy within five days, and cultures of feces negative for the Flexner bacillus were obtained in twenty-two days. This intercurrent infection precipitated another attack of acidosis. The carbon dioxide content of the blood fell to 23 volumes per cent, and the blood sugar rose to 355 mg. per hundred cubic centimeters. On April 20 the insulin required to control acetonuria for a twenty-four hour period reached a total of 2,795 units. With the subsidence of the ketosis, the dose was decreased to about 600 units a day. The blood sugar fell to 75 mg. per hundred cubic centimeters, and the carbon dioxide content of the blood rose to 49.2 volumes per cent.

Five and one-half months after admission the patient's daily insulin requirement was still 350 units. Because of the sudden and unpredictable fluctuations in her diabetic status, it was felt that it could not be satisfactorily controlled at home. She was transferred to the Montefiore Hospital for Chronic Diseases on July 7.

*Laboratory Data.*—During the five month period of observation, considerable clinical and laboratory data were obtained in an attempt to establish the cause of the excessive need for insulin. The following data are presented to illustrate the baffling nature of the problem of insulin insensitivity.

A complete blood count by the hematologist showed a hemoglobin concentration of 65 per cent, 3,900,000 red cells per cubic millimeter and 10,000 white cells per cubic millimeter, with a differential count of 63 per cent polymorphonuclears, 31 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils and 5 per cent reticulocytes. There were 270,000 platelets. The cell volume was 28 per cent. There was no evidence of any blood dyscrasia. Repeated blood counts revealed nothing noteworthy.

Culture of the urine on one occasion revealed *Staphylococcus aureus* (group B) and on another occasion *Streptococcus viridans*. The mild infection of the lower portion of the urinary tract was thought to have followed the numerous catheterizations during the critical period of the patient's illness. The specific gravity of the urine during a concentration test (Fishberg) rose to 1.020. A phenol-sulfonphthalein test showed 35 per cent excretion of the dye within three hours. An intravenous pyelogram revealed nothing abnormal in the upper portion of the urinary tract. There was a moderate degree of hypertrophic arthritis of the lumbar portion of the spine.

Chemical analysis of the blood revealed the following contents per hundred cubic centimeters: serum chlorides from 540 to 690 mg., calcium 8.5 mg., phosphorus 2.9 mg., phosphatase 5 King-Armstrong units, total protein 5.9 Gm., albumin 3.9 Gm. and globulin 2.0 Gm. Repeated determinations did not reveal elevation of the blood urea nitrogen. The icterus index of the blood was 3; the Takata-Ara reaction was 4 plus. The blood cholesterol varied from 300 to 530 mg. per hundred cubic centimeters, with corresponding cholesterol esters between 160 to 340 mg., a normal relation. Oral dextrose tolerance tests showed high diabetic curves.

A roentgenogram of the skull showed a normal sella turcica, no evidence of increased intracranial pressure, a calcified pineal body in normal position and calcification of the parasellar groove of the right internal carotid artery without decrease in the size of the lumen of the vessel. There was no abnormality in the bones. A neurologic consultant did not find evidence of disease of the central nervous system. There was a mild peripheral neuropathy. The spinal fluid, obtained by lumbar puncture, was clear, under normal pressure and contained 4 lymphocytes per cubic millimeter. The Pandy, Wassermann and globulin tests yielded negative reactions. The colloidal gold curve was normal. The spinal fluid contained 48 mg. of protein and 68 mg. of sugar per hundred cubic centimeters. An electroencephalogram showed no abnormality.

Gastric analysis after a Rehfuess test meal showed 60 units of free acid. Examination of the stomach and duodenum after a barium sulfate meal revealed nothing abnormal. A barium sulfate enema showed nothing unusual.

Bromsulphalein tests showed no retention of the dye in the blood stream one hour after injection. The sodium benzoate test of hepatic function likewise gave a normal result. There was no bile in the urine at any time. According to the result of Ehrlich's test a trace of urobilin was present in the urine. As noted previously, the cholesterol partition was normal, and there was no evidence of bilirubinemia at any time.

Repeated roentgenograms of the chest failed to reveal any abnormality in the lungs. The electrocardiogram showed left axis deviation and a deep Q wave in lead IV; the QRS complex was slurred and of high voltage and measured twelve hundredths of a second. The T wave in lead I was diphasic. These changes were interpreted to indicate enlargement of the left ventricle and myocardial damage. Subsequent records showed no significant changes. Venous pressure was 3.5 cm. of blood with no rise on pressure in the right upper quadrant of the abdomen. The saccharin circulation time was seventeen seconds. The basal metabolic rate was +25 per cent on one occasion, +23 per cent after a second trial and then  $\pm 0$  per cent.

*Experimental Data.*—An attempt was made to determine whether there was any substance, antagonistic to insulin, in the patient's blood serum that would affect the insulin depression curves in rabbits. This was carried out by the following two methods:

1. Four and a half cubic centimeters of the patient's serum was mixed with 20 units of insulin, incubated three days at 37 C. and injected intravenously into a fasting 2 Kg. rabbit. The sugar content of the rabbit's blood was determined while the animal was fasting and one-half, one and two hours after injection. Similar parallel control determinations were made using serum from a subject without diabetes (table 2). This method was similar to the one used by Wiener.<sup>1b</sup>

2. Ten cubic centimeters of the patient's serum was mixed with 0.5 unit of insulin and immediately injected into a fasting 2 Kg. rabbit. The sugar content

of the rabbit's blood was determined while the animal was fasting and twenty, forty and sixty minutes after injection. Parallel control determinations were made with insulin alone, the patient's serum alone and a mixture of insulin and serum from a subject without diabetes (table 3).

In the first test the insulin depression curve was affected similarly by the patient's serum and by the control serum. In the second test both serums apparently prevented the hypoglycemia observed when insulin alone was injected.

Both these methods failed to indicate the presence of anti-insulin substances in the patient's serum that were not present in the control serum.

Passive transfer antibody tests (Prausnitz-Küstner) were performed to determine the presence or absence of transferable anti-insulin antibodies or reagins in

TABLE 2.—*Effect of an Incubated Mixture of Serum and Insulin on the Insulin Depression Curve in Rabbits*

Time Relation of Blood Sample to Injection	Blood Sugar, Mg./100 Cc.	
	4.5 Cc. of Patient's Serum Plus 20 Units of Insulin	4.5 Cc. of Serum from a Nondiabetic Subject Plus 20 Units of Insulin
Before injection, rabbit fasting.....	85	100
30 minutes after.....	75	63
60 minutes after.....	75	70
120 minutes after.....	85	85

TABLE 3.—*Effect on a Mixture (Without Incubation) of Serum and Insulin on the Insulin Depression Curve in Rabbits*

Time Relation of Blood Sample to Injection	Blood Sugar, Mg./100 Cc.			
	10 Cc. of Patient's Serum Plus 0.5 Unit of Insulin	10 Cc. of Serum from a Nondiabetic Subject Plus 0.5 Unit of Insulin	0.5 Unit of Insulin Without Serum	10 Cc. of Patient's Serum Without Insulin
Before injection, rabbit fasting.....	125	100	90	105
20 minutes after.....	95	90	65	100
40 minutes after.....	90	95	45	90
60 minutes after.....	90	100	40	90

the patient's serum. These were done by injecting the patient's serum intradermally into a normal subject and twelve hours later injecting insulin intradermally at the same site. Equivocal reactions to regular insulin (Squibb) and crystalline insulin (Stearns) were observed; preparations of protamine zinc insulin (Lilly) and unmodified insulin (Lilly) gave no reactions. Intradermal tests with these types of insulin were unrevealing. No transferable anti-insulin antibody was demonstrated. Results of precipitin tests with the patient's serum against regular insulin were negative.

*Therapeutic Attempts.*—After the insulin dosage had become fairly well stabilized, several attempts were made to reduce the large requirement. The usual diet contained 150 Gm. of carbohydrate, 90 Gm. of protein and 80 Gm. of fat. Trial periods both on high carbohydrate (with carbohydrates to 300 Gm.), low fat or low carbohydrate, high fat diets did not appreciably affect the insulin require-



ment. Trial periods with special beef or pork insulin were not attempted in this case. Such attempts in the case reported by Marble<sup>1d</sup> had no effect on the diabetes.

Because of the well known antagonism between the pancreas and the anterior lobe of the pituitary and in view of several good results of roentgen therapy reported in the literature in cases of similar disorder, it was decided to give the patient a course of such therapy over the region of the pituitary and the hypothalamus. During the third month of her stay in the hospital, the patient was given a course of roentgen therapy over the pituitary region, with a total dose of 1,900 r. This comprised nineteen daily doses of 100 r each alternately over the right and the left temporoparietal region, centering on the pituitary, through a 10 cm. by 10 cm. port. Each dose was delivered at 200 kilovolts and 20 milliamperes, with filters of 1 mm. of copper and 3 mm. of aluminum at a focal skin distance of 60 cm. The daily insulin requirement immediately before the roentgen therapy was 550 units, immediately after it 575 units, two weeks later 600 units, one month later 580 units and two months later 350 units.

During the fourth month lipocaic, a pancreatic extract, which has been claimed to diminish fatty infiltration of the liver and improve hepatic function,<sup>2</sup> was given in doses of 2 Gm. three times daily for thirty-four days. The average daily dose of insulin preceding the giving of lipocaic was about 550 units while after one month of treatment it had fallen to about 350 units.

*Subsequent Course.*—A summary of the clinical course of the patient's illness during the six months following transfer from Mount Sinai Hospital was made available by Montefiore Hospital, where she was treated for that period.

On admission to Montefiore Hospital the patient's history and the results of her physical examination were essentially as previously described. She was given 240 units of protamine zinc insulin once daily. After one week the dose was reduced to 80 units a day. Then the protamine zinc insulin was discontinued, and the patient was given unmodified insulin in doses of 40 to 50 units three times a day. At first her requirement was labile. She had frequent hypoglycemic reactions and on other occasions glycosuria (4 plus) and acetonuria (2 plus) were present. The content of blood sugar varied up to 355 mg. per hundred cubic centimeters, depending on the extent of control of the diabetes. The urine showed albumin (3 plus) and microscopic examination revealed 5 to 10 white cells, 1 to 2 red cells and many granular casts per high power field. The basal metabolic rate was +10 per cent on two occasions. Roentgen examination of the heart showed rounding of the left ventricle and dilatation of the aorta. The lungs were clear. There was spondylitis of the lumbar portion of the spine. A series of roentgenograms of the gastrointestinal tract revealed nothing abnormal in the stomach or small intestine. Hypermotility and streaking of the transverse colon were noted.

In October 1940 the patient had an attack of jaundice associated with pains in the right upper quadrant of the abdomen, nausea and anorexia. The stools were clay colored. The icterus index at this time was 30; the van den Bergh reaction was immediately positive. The cholesterol content of the blood was 334 mg. per hundred cubic centimeters. A diagnosis of toxic hepatitis was made. This episode subsided within three weeks. A series of roentgenograms of the gallbladder made

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2. The Present Status of Lipocaic, preliminary report of the Council on Pharmacy and Chemistry, J. A. M. A. **115**:1454-1455 (Oct. 26) 1940. Dragstedt, L. R.: The Present Status of Lipocaic, *ibid.* **114**:29 (Jan. 6) 1940.

on November 11 was normal. In December the patient's diabetes was well controlled with only 10 units of unmodified insulin a day. The urine contained neither sugar nor acetone. On her discharge from Montefiore Hospital on Jan. 4, 1941, the diabetes was controlled by a salt-poor diet containing 130 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat and a dose of 5 units of unmodified insulin once daily.

The patient returned to Mount Sinai Hospital and has been followed by one of us (H. P.) in the outpatient diabetes clinic. Her appearance was essentially unchanged, and she still complained of weakness and generalized aches and pains. Physical examination revealed nothing new. The blood pressure was 150 systolic and 90 diastolic, measured in millimeters of mercury. The urine showed a trace of albumin, occasional casts and rare red and white blood cells. The hemoglobin concentration was 90 per cent, and the white cell count, 8,400, with a normal differential count. The patient's diabetes has been satisfactorily controlled for the last six months by one daily injection of 5 units of protamine zinc insulin and a diabetic diet containing 150 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat.

#### COMMENT

The condition of an occasional patient with diabetes mellitus refractory to specific replacement therapy with insulin is a fascinating problem. In this case, although the clinical findings furnish no satisfactory explanation for the temporary large insulin requirement, at least three mechanisms, ketotic acidosis, infection and hepatic disease, may have been of etiologic significance and will be discussed briefly. A detailed analysis of the many factors involved in the production of insulin tolerance may be found in papers by Glen and Eaton,<sup>1c</sup> Marble,<sup>1d</sup> Pollack<sup>3</sup> and Martin and associates<sup>1f</sup> and will not be repeated in this report.

During diabetic ketotic acidosis the insulin requirement is increased by some fundamental alteration in carbohydrate metabolism. Apparently a vicious cycle is set up, for as the ketotic state becomes more severe, larger amounts of insulin are needed. In this case moderate ketosis was present for at least three days prior to the onset of the insulin-resistant phase shortly after admission, on a second occasion five weeks after admission and during the episode of diarrhea two months later. With each episode of ketosis the degree of insulin tolerance increased more rapidly than did our willingness to augment the large amounts of the hormone that were being administered. Although incomplete control undoubtedly contributed to these periods of huge insulin need, acidosis cannot explain the sustained high requirement for the entire six month period. In cases of diabetes refractory to insulin reported by Wiener,<sup>1b</sup> Glen and Eaton<sup>1c</sup> and Martin and co-workers<sup>1f</sup> acidosis produced sharp increases in the amounts of insulin required. It is important to emphasize

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3. Pollack, H.: Conditions Associated with Unusual Requirements of Insulin, *Proc. Staff Meet., Mayo Clin.* 8:453-456 (July 26) 1933.

that the appearance of ketonuria in a patient with an abnormally large insulin requirement may herald a degree of insulin insensitivity that may lead to death in diabetic coma unless the ominous significance of the acidosis is realized in time.

Infection causes an increase in the severity of diabetes mellitus and is a common cause of death in patients with the disease. According to Marble,<sup>4</sup> the lowered carbohydrate tolerance during infections may be due to several causes: (1) the lessened production of endogenous insulin, (2) the increased production of hormonal antagonists to insulin, (3) the destruction of insulin and (4) interference with glycogen storage. Menkin<sup>5</sup> has advanced the hypothesis that the increase in proteolysis incident to acute inflammation is responsible for the greater severity of diabetes during infection.

The episode of bacillary dysentery demonstrates the aggravating effect of an infection on the precarious state of carbohydrate metabolism in this case. With the onset of fever and diarrhea, the patient promptly became ketotic and the insulin requirement rose from 600 to 2,795 units. Two days later, when the ketosis had been successfully combated, the daily insulin dose returned to 600 units. The change in insulin requirement was in excess of the clinical severity of the infection and indicated the unstable state of the insulin mechanism. The possibility that a sub-clinical bacillary dysentery was the basis for the entire period of insulin resistance cannot be denied. However, even if this were actually the case, it could only have acted as a precipitating factor to set off a basic abnormality in insulin action, since the result was so extreme.

Patients with diabetes who also have hepatic disease may require larger doses of insulin than the average person with diabetes alone. Thrombosis of the hepatic artery with infarction of the liver was the basis for insulin insensitivity in a case reported by Pollack and Long.<sup>6</sup> Acute hepatitis raised the daily dose of insulin from 30 to 500 units a day in a case described by Root.<sup>7</sup> Cirrhosis usually results in the increased severity of diabetes mellitus, although the exact opposite has been observed also. Hemochromatosis was present in 5 of 26 cases of "insulin resistance" collected by Martin and associates.<sup>1f</sup> In 1 case of

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4. Marble, A., in Joslin, E. P.: *The Treatment of Diabetes Mellitus*, ed. 6, Philadelphia, Lea & Febiger, 1937, p. 407.

5. Menkin, V.: *Diabetes and Inflammation*, *Science* **93**:456-458 (May 9) 1941.

6. Pollack, H., and Long, E. R.: *Thrombosis of the Hepatic Artery with Sudden Resistance to Insulin in a Diabetic Patient*, *Arch. Path.* **13**:530-532 (March) 1932.

7. Root, H. F.: *Acute Hepatitis in a Diabetic with Severe Acidosis and Suppression of Urine*, *New England J. Med.* **212**:545-547 (March 28) 1935.

such a disorder, reported in detail by Root,<sup>8</sup> the patient took 1,680 units in the twenty-four hour period before death in a diabetic coma. Hepatomegaly is a common occurrence in the severe diabetes of childhood. Under such circumstances the hepatic enlargement is due to fatty infiltration. The treatment of such a condition with betaine hydrochloride,<sup>9</sup> pancreatic extract<sup>10</sup> and protamine zinc insulin<sup>11</sup> leads to a decrease in the size of the liver and an improvement in carbohydrate tolerance. Mirsky and his collaborators<sup>12</sup> have demonstrated that the susceptibility to acidosis and coma is increased by a reduction in hepatic glycogen reserves. Himsworth<sup>13</sup> suggested that the liver produced a ferment, insulin-kinase, necessary to activate insulin and that in patients with hepatic disease the formation of the enzyme was reduced, with a concomitant decrease in insulin sensitivity.

Several aspects of this case, particularly the hepatomegaly and the episode of jaundice, raise the question of hepatic disease as the cause of the insulin-refractory state. This factor is difficult to evaluate because in this instance one cannot distinguish between cause and effect. Jaundice occurred when the insulin requirement had almost returned to usual levels and may have been the result rather than an indication of the cause of the defective insulin activity. Hepatic function tests (bromsulphalein excretion, sodium benzoate excretion and cholesterol partition), performed when the insulin-refractory phase was at its height, did not confirm the existence of hepatic damage. The clinical improvement following a course of lipocaic,<sup>2</sup> which diminishes fatty infiltration in depancreatized dogs may be cited as evidence of a hepatic effect. Evaluation of possible influence of this substance, especially in this case, is extremely difficult for reasons which will be mentioned later. It is our impression that there was only slight evidence that hepatic dysfunction was a pathogenic factor in this case of insulin insensitivity,

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8. Root, H. F.: Insulin Resistance and Bronze Diabetes, *New England J. Méd.* **201**:201-206 (Aug. 1) 1929.

9. White, P.: Diabetes in Childhood, in Joslin, E. P.: *Treatment of Diabetes Mellitus*, ed. 6, Philadelphia, Lea & Febiger, 1937, p. 587.

10. Grayzel, H. G., and Radwin, L. S.: Hepatomegaly in Juvenile Diabetes Mellitus Treated with Pancreatic Extract, *Am. J. Dis. Child.* **56**:22-32 (July) 1938.

11. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, *J. A. M. A.* **106**:914-916 (March 14) 1936.

12. Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: The Hepatic Glycogen Reserves in Diabetes Mellitus, *Endocrinology* **28**:358-367 (March) 1941.

13. Himsworth, H. P.: The Activation of Insulin, *Lancet* **2**:935-936 (Oct. 29) 1932.

although the possibility of a partial and obscure derangement of hepatic function is difficult to exclude on the basis of the available data.

The failure to demonstrate anti-insulin activity in the serum of this patient by the methods described does not disprove the existence of this property. Only a few tests were performed, and the proper technic for the demonstration of an insulin-neutralizing substance in the serum may not have been used. However, Wiener<sup>1b</sup> and Martin and co-workers,<sup>1f</sup> using comparable methods, were also unable to detect a serum antagonist to insulin. On the other hand, Karelitz, Cohen and Leader<sup>14</sup> showed that normal blood and blood from a person with diabetes both inactivate insulin and that the latter did so to a greater extent. De Wesselow and Griffiths<sup>15</sup> obtained similar evidence in elderly persons with diabetes and suggested that the substance in the blood of these patients that affected the insulin depression of blood sugar curves in rabbits was of pituitary origin. Glen and Eaton<sup>1c</sup> induced an active insulin antagonism in rabbits by injections of serum from a patient with insulin insensitivity. The antagonism was more marked if the patient had been given insulin before serum was withdrawn for the test.

The management of our patient involved two distinct problems, the control of the acute alarming episodes of ketotic acidosis and the amelioration of the persistent insulin-refractory state. Each problem was of considerable interest and will be discussed separately.

The chief therapeutic agents during ketosis were insulin, physiologic solution of sodium chloride, lactate-Ringer's solution and dextrose solution. In view of the patient's age, the evidence of arteriosclerosis, the hypertension and the electrocardiographic findings, the cautious use of intravenous therapy seemed justified to prevent an overloading of the circulation. Sufficient dextrose was given to maintain glycosuria. The guide for the administration of insulin was the presence of acetone and dextrose in the hourly specimens of urine and the general condition of the patient. In the presence of persisting acetonuria, the dose of insulin was increased rapidly until an effective level was reached at 200 units per hour for ten hours. We were prepared to raise the dose to higher levels on the assumption that control would be effected eventually if enough insulin were administered. When sufficient insulin was given, the acetonuria subsided and in the presence of overdosage of insulin, hypoglycemic reactions resulted. The results were similar to those ordinarily obtained in diabetic persons except that the amounts of

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14. Karelitz, S.; Cohen, P., and Leader, S. B.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro, *Arch. Int. Med.* **45**:546-558 (April) 1930.

15. de Wesselow, O. L. V., and Griffiths, W. J.: On the Possible Role of the Anterior Pituitary in Human Diabetes, *Lancet* **1**:991-994 (May 2) 1936.

insulin required were enormous. Perhaps, the administration of the total amount of insulin required in a shorter time would have resulted in a more prompt response to therapy. This experience supports the concept of Taussig<sup>16</sup> that in cases of insulin insensitivity the law of mass action of inorganic chemistry is valid with respect to the action of insulin. As stated by Martin and associates<sup>1f</sup>: "There is not necessarily any upper limit to the number of units of insulin that may be given." The chief therapeutic aim is to give enough of the hormone.

The following methods have been used to reduce the insulin requirements of patients to whom it is necessary to administer excessively large amounts of the hormone: changes in diet; change in the type of insulin<sup>1c</sup>; intravenous administration of phosphates<sup>1d</sup>; therapy with various endocrine substances, particularly dihydroxyestrin (estradiol)<sup>17</sup>; a low potassium diet<sup>1e</sup>; desensitization procedures,<sup>18</sup> and roentgen therapy to the pituitary area.<sup>19</sup>

In this case a trial of roentgen therapy over the pituitary was carried out. This method of treatment has been reported to have reduced large insulin requirements in a few cases.<sup>20</sup> Failures of irradiation of the pituitary to influence the amount of insulin required for control of diabetes in human beings and in dogs have also been recorded.<sup>21</sup> Although there was no clinical evidence of disease of the pituitary in this case, it was felt that if it was possible to depress the activity of the anterior lobe, some benefit might result, since the anterior lobe of

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16. Taussig, A. E.: A Case of Diabetes Mellitus Refractory to Insulin, *Tr. A. Am. Physicians* **42**:166-178, 1927.

17. Footnote 1 *c* and *e*.

18. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, *J. Lab. & Clin. Med.* **18**:1203-1211 (Sept.) 1933.

19. (a) Pieri, J., and Sarradon, P.: Diabète grave insulino-résistant. Réduction notable de l'insulino-résistance par la radiothérapie hypophysaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:1579 (Dec. 2) 1935. (b) Merle, E.: Diabète grave insulino-résistant. Réduction brusque et massive de l'insulino-résistance par irradiation de la région hypophysaire, *ibid.* **51**:35 (Jan 21) 1935. (c) Cannavò, L.: Insulinoresistenza e irradiazioni roentgen della regione ipofisaria, *Policlinico (sez. prat.)* **43**:1099 (June 15) 1936; abstracted, *J. A. M. A.* **107**:541 (Aug. 15) 1936. (d) Barnes, B. O.; Culpepper, W. L., and Hutton, J. H.: Experimental Diabetes Treated by X-Ray Applied to the Pituitary and Adrenal Regions, *Am. J. Physiol.* **113**:7 (Sept.) 1935. (e) Selle, W. A.; Westra, J. J., and Johnson, J. B.: Attempts to Reduce the Symptoms of Experimental Diabetes by Irradiation of the Hypophysis, *Endocrinology* **19**:97-104 (Jan.-Feb.) 1935. (f) Pijoan, M., and Zollinger, R.: Observations on Carbohydrate Metabolism Following Irradiation of the Pituitary Gland, *ibid.* **21**:357-360 (May) 1937.

20. Footnote 19 *a*, *b*, *c* and *d*.

21. Footnote 19 *e* and *f*.

the pituitary and the pancreas have been shown to be antagonists with respect to carbohydrate metabolism. There was noticeable improvement three months after the completion of this therapy. In view of the complete subsidence of the insulin-resistant state during the subsequent three months, the possibility that roentgen therapy may have been responsible for this improvement cannot be excluded. However, judgment must be reserved, since spontaneous remission has been known to occur and because lipocaic was administered for five weeks after roentgen therapy was completed.

Lipocaic, a fat-free alcohol extract of pancreas, has been reported as a specific substance which on oral administration to depancreatized dogs decreases the fat in the blood, the fatty infiltration of the liver and the insulin requirement.<sup>2</sup> In this case 2 Gm. of lipocaic taken daily for thirty-four days was associated with a decrease in the size of the liver and a reduction of the insulin requirement. Unfortunately, the efficacy of this therapy cannot be established with any degree of certainty in view of the previous roentgen therapy.

The complete regression of insulin resistance of the intensity and the duration observed in this case is not common. Of 26 cases collected by Martin and associates,<sup>1f</sup> death occurred in 12 despite therapy, as happened in the case which the authors themselves reported, making the mortality 48 per cent in this group. Subsidence of a severe insulin insensitivity was observed by Wiener,<sup>1b</sup> whose patient required 3,250 units of insulin in twenty-four hours while in diabetic coma and was given 142,000 units of insulin in twelve weeks. Three years later this patient was well and required only 50 units of insulin daily. No special treatment was administered to effect this change.<sup>22</sup> In the case reported by Glassberg, Somogyi and Taussig<sup>1a</sup> the patient required 26,000 units of insulin, with peaks of 1,000 and 1,100 units in twenty-four hours, during a three month period of observation. Two months later the daily insulin dose was 100 units. At the present time, fourteen years after the episode of refractoriness to insulin, this patient's diabetes is well controlled by 50 units of regular insulin taken daily in two doses.<sup>23</sup> Cases of this type indicate that insulin insensitivity may be temporary and that the chief indication is to furnish sufficient insulin for long enough periods to allow the refractory phase to terminate. Death in coma seems avoidable if large enough doses are given as severe emergencies arise.

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22. Dr. Herbert J. Wiener, New York, informed us of the subsequent course of his patient and permitted us to include the information in this report.

23. Dr. A. E. Taussig, St. Louis, provided the follow-up note on his case and permitted us to make the statement of the present status of his patient.

SUMMARY

A case of diabetes mellitus in which the insulin requirement was extremely high is presented. More than 85,000 units of insulin was administered in a five and one-half month period of observation. During episodes of ketotic acidosis it was necessary to give 2,360 units, 2,500 units and 2,795 units of insulin in twenty-four hours before adequate control was accomplished. No definite cause for the insulin-refractory state could be determined. Therapeutic procedures included roentgen irradiation over the pituitary and the administration of lipocaic. It was not possible to establish a definite relation between these forms of therapy and the improvement which followed their use. The excessive insulin need subsided six months after its onset, and the patient remained mildly diabetic for the subsequent six months.

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# NEUROPSYCHIATRIC DISTURBANCES IN INTERNAL DISEASE \*

METABOLIC FACTORS AND ELECTROENCEPHALOGRAPHIC CORRELATIONS

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Clinical manifestations of disease are in the final analysis the result of altered physiologic or biochemical relations. This is true whether one observes the direct evidence of abnormal function or the compensatory reactions invoked to counteract abnormal forces. The central nervous system is no exception to this principle. And this is no less true whether one deals with disease directly involving the central nervous system or with the effects on it of disease having its origin elsewhere. This report is concerned with secondary effects. Neuropsychiatric complications of underlying disease may vary widely from mild aberrations of normal mood and behavior to sweeping disturbances that dominate the entire clinical picture and may obscure the disease itself.

The basis for these reactions depends primarily on the fundamental nature of brain metabolism. The central nervous system has the most exacting metabolic requirements in the body. Unlike other tissues, it is primarily aerobic in its metabolism, and it is unable to establish a significant oxygen debt. Sensitivity to oxygen lack is greatest in the cerebral cortex, which suffers irreversible damage in five to eight minutes of complete oxygen deprivation, while the medulla and spinal cord fail in twenty

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\*Parts of this material were presented at a meeting of the New York Neurological Society, Dec. 3, 1940 (Margolin, S. G.; Strauss, H., and Engel, G. L.: Electroencephalographic Changes Associated with Hypersensitivity of the Carotid Sinus, *Arch. Neurol. & Psychiat.* **45**:889 [May] 1941. Engel, G. L., and Margolin, S. G.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, *ibid.* **45**:890 [May] 1941) and at a meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society, Jan. 7, 1941 (Engel, G. L., and Margolin, S. G.: Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in Production of Abnormal Cerebral Function, *ibid.* **45**:881 [May] 1941).

to thirty minutes.<sup>1</sup> Other tissues can survive complete oxygen lack for hours. Carbohydrate provides the major substrate capable of sustaining normal activity. Fat and protein derivatives cannot be substituted for dextrose.<sup>2</sup> The respiratory quotient of the mammalian brain is 1.0.<sup>3</sup> Storage of carbohydrate as glycogen is extremely small and does not represent a significant reserve.<sup>5</sup>

Closely correlated with its metabolism is the electrical activity of the brain. The electroencephalograph records brain potentials through the scalp and thereby reflects the behavior of the brain in its internal environment. Changes in metabolic factors, such as oxygen tension or availability of dextrose, are quickly reflected in the electroencephalogram.<sup>6</sup> Sensitivity to oxygen lack is exquisite, fourteen to fifteen seconds of complete anoxia being sufficient to abolish completely the electrical activity of the cortex.<sup>6b</sup> Shifts in electrolyte balance,  $p_H$  and particularly carbon dioxide tension significantly influence the brain waves.<sup>7</sup> This prompt response to alterations in the internal environment of the brain provides a convenient means by which the physiologic effects of disease in remote areas may be detected and correlated with clinical observation.

In this report we are concerned chiefly with processes which interfere with proper transport and utilization of oxygen and dextrose, the two most important substances involved in cerebral metabolism. Only representative cases in each group are presented. Naturally, this covers only a small proportion of etiologic factors, but in principle a fundamental pathophysiologic basis for a more general phenomenon is provided.

1. McFarland, R. A.: The Effects of O<sub>2</sub> Deprivation (High Altitude) on the Human Organism, Technical Development Report III, United States Civil Aeronautics Authority, May 1938.

2. Corcoran, A. C., and Page, I. H.: Carbohydrate Metabolism of Brain, *Enzymologia* **9**:10, 1940.

3. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, *Am. J. Physiol.* **101**:446, 1932.

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## OXYGEN LACK

Insufficient oxygenation for cerebral needs may result from cerebral anemia, in which the blood supply is diminished, and from cerebral anoxemia, in which the oxygen saturation of the blood is inadequate for cerebral needs. These two conditions cannot always be sharply divided. Both may be observed in the acute and the chronic state.

*Acute Cerebral Anemia.*—Acute cerebral anemia is usually due to sudden alterations in the general or the local circulation. When change is general, the manifestations are likely to be brief and to occur in the erect posture. Etiologic factors are many, but only those types which can be easily reproduced lend themselves readily to study. Hypersensitivity of the carotid sinus reflex is a convenient example which can be used in the study of a rather general phenomenon.

Thirty instances of hypersensitive carotid sinus reflex were observed. In 22 cases the patients complained of episodes of weakness, dizziness, faintness, confusion or syncope. These symptoms could be reproduced by massage or compression of the carotid sinus. Of this group, 21 cases were found to represent the cardioinhibitor (vagal) type of reflex. This reaction could be abolished by atropine. In the twenty-second case the patient had a pure depressor type, syncope following a marked fall in blood pressure, without slowing of the pulse. This could not be prevented by atropine, ephedrine, alpha-N-dimethyl-p-hydroxyphenethylamine (paredrinol), p-hydroxy-*a*-methylphenethylamine (paredrine), amphetamine or desoxycorticosterone acetate. Both of these types represented instances in which a sudden change in cardiovascular dynamics precipitated a critical decrease in cerebral blood flow.

Simultaneous electroencephalographic and electrocardiographic tracings were obtained in 7 cases of the vagal type, and in 1 case of the depressor type, of hypersensitive carotid sinus reflex during stimulation and before and after the administration of atropine. In the vagal group stimulation resulted in the development of an asystole of two to thirteen seconds. Onset of asystole was usually followed by hyperpnea and then by the characteristic clinical manifestations of weakness, faintness, dizziness, confusion and syncope. Simultaneously, the electroencephalogram revealed a diffuse, unlocalized burst of irregular, 3 to 6 per second waves of moderate potential, persisting for a few seconds and sometimes followed by a period of random low voltage activity. In a few cases when asystole was unusually prolonged syncope would be followed by a generalized convulsion. In such instances the electroencephalogram showed rapid high potential spikes, probably of muscle origin, superimposed on the slow waves. When the vagal cardioinhibitor reflex was blocked by atropine, no symptoms or electroencephalographic changes occurred. In the case of the depressor reflex similar electroencephalographic changes

were noted. These coincided with the development of symptoms and occurred during the rapid fall in blood pressure. Hyperpnea was again the first reaction. In all these cases the development of symptoms was more prompt and constant in the erect position.

In all the remaining 8 cases the patients exhibited symptoms that were suggestive of involvement of the central nervous system. These included focal or generalized convulsions, episodes of aphasia, motor weakness and dysesthesias. Neurologic examinations revealed nothing significant. Manual stimulation of the carotid sinus reproduced symptoms which were specific and constant in each case. In this group even when bradycardia or asystole occurred and was abolished by atropine, the characteristic neurologic reaction still took place on massage of the carotid sinus in spite of the absence of change in pulse or blood pressure. Electroencephalograms were made in 7 cases. As in the previous group, stimulation of the carotid sinus was followed by bursts of slow potentials during which the clinical manifestations characteristic for each patient occurred. No clinical manifestations became apparent unless the electroencephalographic changes occurred. The characteristic specificity of focal responses in the presence of a diffuse dysrhythmia suggested that in these cases there was an underlying focal area of diminished threshold which became clinically manifest if the reaction was not dominated by syncope or a generalized convulsion.

A hypersensitive carotid sinus reflex is generally secondary to disease directly or indirectly involving some portion of the reflex arc. Thus, it is frequently associated with generalized, cerebral and coronary arteriosclerosis and with local disease of the carotid arteries.<sup>8</sup> The cardio-inhibitor type is sometimes associated with disease of hollow viscera, notably the gallbladder.<sup>9</sup> When neurologic symptoms are found to be reproducible by stimulation of the carotid sinus, other primary etiologic factors must still be considered.

Two illustrative cases are briefly presented.

CASE 1.—S. S., a 46 year old man, had had a cholecystectomy performed four years before admission, because of epigastric pain, nausea, vomiting, icterus and acholic stools. At operation, the gallbladder and the cystic duct contained stones and the common duct contained chalky material. After operation the patient adhered to a low fat diet and was well for one and a half years. He then had a recurrence of attacks of epigastric pain, associated with nausea, belching and marked dizziness and faintness. There was no recurrence of icterus.

Examination on admission revealed nothing unusual. The blood pressure was 110 systolic and 70 diastolic. A well healed scar was present in the right upper

8. Ferris, E. B.; Capps, A. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* 14:377, 1935.

9. Engel, G. L., and Engel, F. L.: *New England J. Med.*, to be published.

quadrant of the abdomen. There was no abdominal tenderness or masses. The electrocardiogram was normal. Roentgen examination of the abdomen failed to yield evidence of a radiopaque biliary calculus.

Stimulation of the right carotid sinus caused an asystole of five to six seconds, hyperpnea, pallor, dizziness and faintness, followed by nausea, belching and lacrimation. These symptoms were identical with those occurring during the bouts of pain. The reaction was abolished by atropine. A duodenal tube was passed, and 20 cc. of olive oil was introduced, with a good flow of bile resulting. For two days after this it was not possible to produce any response to massage of the carotid sinus. When sensitivity had returned, the patient was given a high fat diet. This was followed by a decrease in the activity of the carotid sinus reflex and considerable relief of symptoms.

Comment: This case is representative of the first group, in which a vagal type of reflex was apparently responsible for the episodic dizziness and faintness that accompanied the attacks. In this instance the sensi-

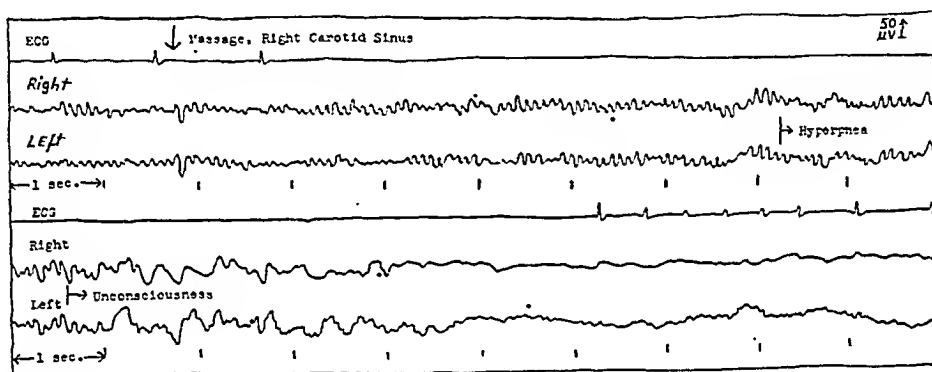


Fig. 1.—Simultaneous electroencephalogram and electrocardiogram in a case of hypersensitivity of the carotid sinus reflex of the vagal type.

tivity of the carotid sinus reflex appeared to be related to a postcholecystectomy syndrome.

CASE 2.—H. Z., a 46 year old dentist, at the age of 12 had suffered an injury to the skull followed by loss of vision in the left eye. For ten years he had noted episodes of precordial pain and for two years had had fluctuating hypertension. Five months before admission he had abruptly become aware of sudden weakness occurring about ten minutes after arising in the morning. At the same time he had begun to have frequent episodes of involuntary clonic movements of the right hand and arm, which came without warning and were unrelated to any particular activity. Unassociated with this were transitory paresthesias of varying extent in the fingers of the right hand, occasionally involving the arm and the right half of the body.

On physical examination the patient appeared well developed and well nourished. The left eye showed optic atrophy, corneal scars and a left divergent strabismus. The heart and lungs were normal. The blood pressure was 140 systolic and 70 diastolic in the right arm and 105 systolic and 90 diastolic in the left arm. A systolic thrill and bruit were detectable in the left supraclavicular fossa. Numerous subcutaneous nodules, ranging from the size of a millet seed to 1 cm. in diameter,

many of which were attached to tendons, were noted. Neurologic examination revealed nothing abnormal except slight diminution of sensation for all modalities over the dorsum of the left hand.

Laboratory Data: The blood contained 500 mg. of cholesterol and 250 mg. of cholesterol ester per hundred cubic centimeters. Biopsy of a subcutaneous nodule revealed fibroxanthoma. Roentgen examination of the skull and the cervical portion of the spine showed no abnormalities. An electrocardiogram revealed normal sinus rhythm and a diphasic T wave in lead IV. Pneumoencephalography revealed moderate symmetric dilatation of the ventricular system.

Manual stimulation of the carotid sinus resulted in asystole, followed by dizziness, weakness and a focal clonic seizure involving the right upper extremity. Prolonged stimulation caused the seizure to become generalized. Atropine abolished the vagal effect, but the abnormal neurologic response and the abnormal electroencephalographic changes persisted in the absence of changes in pulse and blood pressure on massage of the carotid sinus.

Comment: This case belongs in the second group. The clinical and laboratory data justified a diagnosis of xanthomatosis. The hypersensitive carotid sinus and the focal neurologic manifestations were probably associated with the generalized vascular disease that accompanies xanthomatosis.

*Acute Cerebral Anoxemia.*—Acute anoxemia of sufficient extent to cause cerebral symptoms is most often a fatal complication. Instances of recurrent severe cerebral anoxemia are rare. The following case is a unique example of this condition:

CASE 3.—R. I., a 15 year old girl, had a congenital cardiac lesion which had been recognized early in life. Convulsions and periods of unconsciousness had first occurred when she was a few months old. At the age of 5 years syncopal seizures had become frequent and thereafter had incapacitated her. These attacks occurred on slight exertion, on excitement and sometimes after prolonged fasting. During the attacks the patient was unconscious for one to two minutes. In the month preceding admission the patient had had at least one such spell a day.

On physical examination the patient appeared thin but well nourished. There was slight cyanosis at rest. Clubbing of the fingers and toes had occurred early. The lungs were clear. The heart was enlarged to the left and the right. The point of maximal impulse was in the sixth interspace, 11 cm. from the midline. A loud harsh murmur extended throughout systole, heard along both borders of the sternum, loudest in the third and the fourth interspace to the left. The second pulmonic sound exceeded the second aortic sound. The blood pressure was 120 systolic and 80 diastolic. Neurologic examination revealed nothing abnormal.

The report of the roentgen examination was as follows: "The heart was globular. The aorta was somewhat widened, and the pulmonary artery appeared small, suggesting the presence of pulmonary stenosis; the apex of the heart appeared unusual, being rounded and showing slight angulation, suggesting that its lower portion consisted of right ventricle."

An electrocardiogram showed regular sinus rhythm, marked right axis deviation and a QRS interval of high voltage. The carotid sinus reflex was not hypersensitive, and there was no postural hypotension.

In the ward the patient had several syncopal seizures, which were noted to occur with fear, pain, excitement and the exertion of getting out of bed. Each attack was marked by tachycardia (rate 150 to 170), which an electrocardiogram

revealed to be regular and of sinus origin. The sequence of events was, first, tachycardia, followed by increasing dyspnea and intense cyanosis and then confusion, stupor and unconsciousness. If the unconsciousness persisted for more than a minute, the patient showed clonic movements of the extremities, conjugate deviation of the eyes and rigidity. Slowing of the pulse and decrease in cyanosis always accompanied recovery. Headache and somnolence followed such attacks.

An electroencephalogram made with the patient at complete rest was entirely normal (fig. 2). After she walked 30 steps slowly, her pulse rate was 160 per minute and she was markedly cyanotic and dyspneic and somewhat dazed, torpid and confused. The electroencephalogram taken immediately showed instead of normal rhythm, slow irregular high potential delta waves (fig. 2). The record returned to normal in three and a half minutes as the patient recovered.

Comment: The clinical and roentgen findings suggested a diagnosis of tetralogy of Fallot. The mechanism of the seizures was thought to be as follows: At complete rest the heart was just capable of meeting tissue oxygen requirements, as indicated by the slight degree of cyanosis

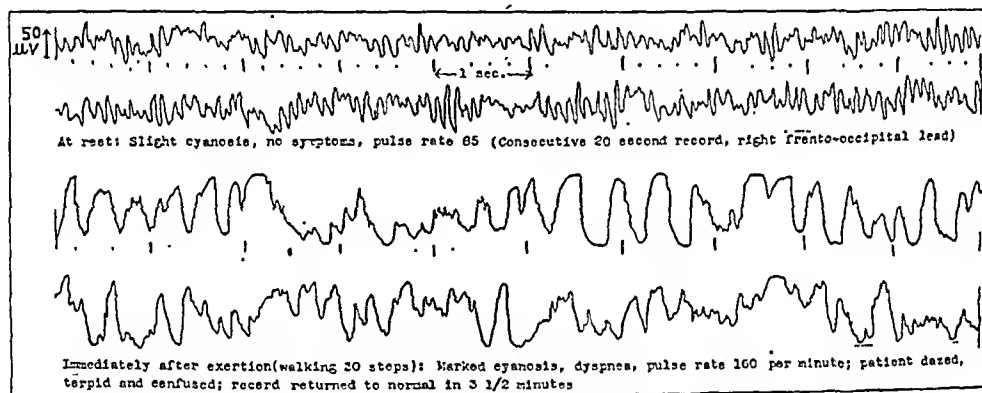


Fig. 2.—Electroencephalogram in a case of acute cerebral anoxemia.

and the normal electroencephalogram. During tachycardia, produced by any cardioaccelerator stimulus, such as exertion, fear or pain, the nature of the congenital defect prevented adequate quantities of fully oxygenated blood from reaching the tissues. The resultant anoxia in itself tended to increase the tachycardia. The ensuing picture was the direct result of acute cerebral anoxemia. Compensation was restored only when the cardiac rate was again slowed.<sup>9a</sup>

9a. Recently there has come to our attention a case of an almost identical condition reported by Hunter, in 1783 (*M. Obs. Soc. Physicians London*, 6:299, 1784). The patient in this case was an 8 year old boy, whom Hunter observed until his death at the age of 13. To quote directly from the author's report: "His [the boy's] complexion had never been fresh, but always dark, or tending to black. . . . The most distressing symptoms were fits, which were always alarming, sometimes more violent and more frequent than at other times, and in general worse when he was in town than in the country; for which reason he was kept for some years almost constantly at his father's country seat. When the fit was coming upon him, he was

*Chronic Cerebral Anoxemia.*—The typical syndrome of chronic cerebral anoxemia is most commonly found in the end stages of chronic asthma and bronchitis, when the compensatory devices have reached their limit. Four cases in this category were observed. The ages of the patients ranged from 52 to 69 years. All gave a history of bronchitis and asthma of many years' duration and of increasing dyspnea and cyanosis preceding admission. All showed marked emphysema and diminished vital capacities, ranging from 800 to 1,300 cc. Marked secondary polycythemia was present, the red cell count ranging from 6,640,000 to 7,480,000 per cubic millimeter. The blood volumes of 2 of these patients were 159 and 167 cc. per kilogram, respectively, almost double normal. In 1 patient the arterial oxygen saturation was only 85.9 per cent three weeks before death. Compensation had begun.

In only 1 of these 4 cases did the patient survive. In all cases the patients had pulmonary decompensation precipitated by an acute infection of the respiratory tract. All patients entered the hospital with acute right-sided heart failure and with intense respiratory distress. The heart failure and the infection responded to specific therapy, but a predominantly cerebral syndrome persisted. Two of the patients had collapsed just prior to entry. At first the patients showed somnolence, torpor and confusion. They could be aroused, answer simple questions and obey simple commands. The 1 surviving patient overcame her pulmonary infection at this stage and thereafter recovered. In the others stupor gradually deepened, accompanied by a marked slowing of all activities and occasional clonic twitches. This and then by rigidity, hyperreflexia, leading to absent deep reflexes; loss of passing to absent deep reflexes; loss of respiratory, cough and gag reflexes, and finally incontinence of urine and

commonly sensible of it: he grew oppressed at his heart, became weak or faint, grew dark in his colour, and at last almost black, fell down, and seemed insensible. He commonly soon came out of the fit, with sobbing and yawning, and a sense of fatigue. Any hurry upon his spirits, or brisk motion of his body, would generally occasion a fit. And for some of the last years of his life, he had found out, by his own observation, that when the fit was coming upon him, he could escape it altogether, or at least take considerably from its violence or duration, by instantly lying down upon the carpet, on his left side, and remaining immovable in that position for about ten minutes." Hunter was fortunate in obtaining an autopsy. ". . . The cause of his complaint was then very apparent. There was a singular conformation of the heart, which allowed only a very small portion of the blood to pass through the lungs. That peculiarity was partly in the pulmonary artery, which was so small at its beginning from the right ventricle, that it would barely give passage to a small probe. But there was another peculiarity . . . viz. the septum cordis was deficient, or perforated at the basis of the heart; so as, in the dead body, to allow my thumb (a small one) to pass across, from either ventricle to the other, the orifice of the aorta being situated so close to this perforation, as, in the action of the heart, to receive the blood from the right ventricle as well as from the left." This, of course, is a description of the combination of congenital defects now known as the tetralogy of Fallot.



feces. The suppression of the cough and the respiratory reflex established a vicious cycle that terminated in death one to two weeks from the time of entry.

In the case with recovery the electroencephalogram showed a regular rhythm, with a frequency of 7.5 to 8.0 per second, which is at the lower range of normal. In the remaining cases the electroencephalogram showed diffuse, slow, high potential waves, which were uninfluenced by opening the eyes, and a complete absence of normal alpha waves. In the earlier stages of anoxemia the waves were 5 to 6 per second in frequency and were fairly regular. With progression of the anoxic process the record became increasingly disorganized (fig. 3, compare the record in case 4 to that in case 29). It was not possible to change the electroencephalogram or improve the patient's condition by the inhalation of 100 per cent oxygen.<sup>9b</sup>

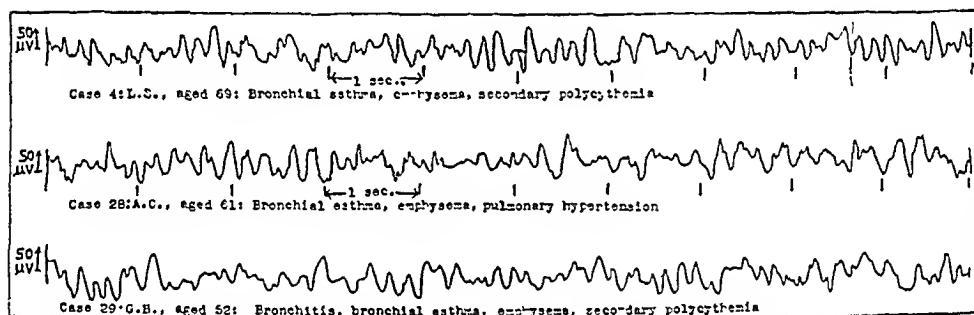


Fig. 3.—Electroencephalograms in cases of chronic cerebral anoxemia.

The following was typical of the group:

CASE 4.—L. S., a 69 year old man, had had severe asthma for many years. For several weeks he had noted increasing dyspnea and frequent asthmatic attacks. Two days before admission he had become much more dyspneic, and the next day edema of the legs and abdomen had appeared. Sudden collapse led to his admission to the hospital.

On physical examination the patient was acutely ill, with intense, black cyanosis and marked dyspnea. The mucous membranes were congested and cyanotic. The pharynx was injected, and there was a postnasal drip of thick, purulent material. The veins of the neck were distended, and there was a hepatojugular reflux. The chest was markedly emphysematous. The breath sounds were distant and accompanied by many sibilant and sonorous rales throughout the sticky moist rales at the bases of both lungs. There was dullness at the base of the left lung. The heart was enlarged to the left and the right. The second pulmonic sound was accentuated. The blood pressure was 170 systolic and 110 diastolic. The liver

9b. Recent studies by one of us (G. E.), making use of a more quantitative method of analysis of the electroencephalogram, have revealed that a significant degree of improvement in the electroencephalogram occurs on inhalation of 100 per cent oxygen in chronic anoxemia of pulmonary origin if the arterial oxygen saturation can be significantly raised.

was enlarged, and there was pitting edema of the legs to a point above the knees. The deep reflexes were hyperactive. The patient was torpid and responded slowly.

Laboratory examination of the blood revealed the hemoglobin concentration to be 126 per cent; the red cell count, 7,480,000 per cubic millimeter; the white cell count, 8,000, with a shift to the left; the urea nitrogen, 15 mg. per hundred cubic centimeters, and the carbon dioxide combining power, 91.5 volumes per cent. The venous pressure was 10.5 cm. of water, with a rise to 16 cm. on compression of the right upper quadrant of the abdomen. The saccharine circulation time was eighteen seconds, and the ether circulation time, eleven seconds. The vital capacity was 1,000 cc. The electrocardiogram showed left axis deviation, prominent P waves and slurring of the QRS interval in lead I.

Heart failure quickly subsided with the use of mercupurin and the limitation of fluids. However, the patient remained intensely cyanotic even with 100 per cent oxygen given by the Boothby-Loyelace-Bubulian mask. Torpor increased, but the patient could be aroused. All movements and reactions to stimuli became markedly slowed. The deep reflexes became depressed and then extinguished. There was marked muscle weakness. Respirations became more shallow; the cough reflex diminished, and he was unable to bring up the thick bronchial secretions. Multiple areas of atelectasis developed. Administration of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) and bronchoscopy were ineffective, and after eleven days the patient became comatose and incontinent; he died on the thirteenth day of hospitalization.

An electroencephalogram was taken on the sixth day of his stay in the hospital, when he still could be easily aroused but showed marked retardation. It revealed fairly regular 5 to 6 per second waves of moderately high potential, which were uninfluenced by opening or closing the eyes (fig. 3, case 4).

#### ABNORMAL CARBOHYDRATE METABOLISM

Abnormal carbohydrate metabolism provides the basis for neuro-psychiatric disturbances in another group of cases. Two types of disorder are considered. The first, Addison's disease, is an endogenous deficiency state with a well defined disturbance in carbohydrate metabolism and is represented by 8 cases. The second group of 5 cases includes a variety of toxic and deficiency states in which the chief evidence for disordered carbohydrate metabolism is a flat sugar tolerance curve with hypoglycemia but in which the nature of this disturbance is not always clear.

*Addison's Disease.*—The presence of a definite defect in carbohydrate metabolism which can be ameliorated by adequate replacement therapy makes Addison's disease an ideal condition for the study of cerebral response to faulty carbohydrate usage. The main features concerning carbohydrate metabolism in Addison's disease may be summarized as follows:<sup>10</sup> (a) slightly impaired absorption of dextrose from the gastrointestinal tract; (b) decreased ability to form new dextrose from the

10. (a) Long, C. N. H.; Katzen, B., and Fry, E.: *The Adrenal Cortex and Carbohydrate Metabolism*, *Endocrinology* 26:309, 1940. (b) Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: *Carbohydrate Metabolism in Addison's Disease*, *J. Clin. Investigation* 19:813, 1940.

intermediary products of carbohydrate and of protein metabolism; (c) a corresponding increase in the utilization of exogenous carbohydrate at the expense of fat and protein, indicated by an elevated respiratory quotient and an increased carbohydrate appetite; (d) rapid exhaustion of available carbohydrate stores, including liver glycogen, particularly under fasting conditions; (e) markedly increased sensitivity to factors which normally lower the level of blood sugar, such as insulin or fasting, with failure of normal homeostatic mechanism to counteract the resultant hypoglycemia, and (f) a tendency to a low value for blood sugar during fasting and a flat sugar tolerance curve with terminal hypoglycemia.

This type of metabolic disturbance, involving both inadequate supply and inefficient utilization of dextrose, clearly represents more than simple hypoglycemia. In patients with Addison's disease symptoms of hypoglycemia may develop at much higher levels of blood sugar than in normal persons,<sup>10b</sup> suggesting that the threshold of cerebral reaction has been lowered. Under such circumstances it is not unexpected that neuropsychiatric disturbances are encountered commonly in persons with this disease. This was first pointed out in the original description by Addison, in 1855,<sup>11</sup> who thought these manifestations resulted from disturbed cerebral circulation. Some of the earlier observers were so impressed with this aspect of the disease that they considered the illness primarily one of the nervous system.<sup>12</sup> Klippel discussed the *encéphalopathie addisonienne*.<sup>13</sup> Hartman<sup>14</sup> repeatedly called attention to the nervous manifestations of the disease and was certain that the vital hormone affected the nervous system directly.

The incidence of neuropsychiatric disturbances in patients with Addison's disease is higher than is ordinarily realized. Of the 25 cases of this condition on record at Mount Sinai Hospital during the past ten years, signs and symptoms in 16 were striking enough to deserve comment (table 1). Review of the literature confirmed this impression! Most commonly these manifestations occur preceding or during crises and may include the widest range of abnormalities. Changes in mood or behavior not infrequently constitute the earliest clinical evidence of impending collapse. In other cases recurrent spells of bizarre behavior or episodic neurologic disturbances occur, with relatively free intervals between.<sup>13</sup> And there are a group of cases on record with sweeping disturbances of long standing, which show marked fluctuations from

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11. Addison, T.: On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules, London, S. Highley, 1855.

12. Greenhow, E. H.: On Addison's Disease, London, Longmans [and others], 1875.

13. Klippel, M.: Encéphalopathie addisonienne, Rev. neurol. 7:898, 1899.  
Lebrun, R.: Contribution à l'étude de l'encéphalopathie addisonienne, Thesis, Paris, 1937.

14. Hartman, F.: The Adrenal Problem, Endocrinology 19:633, 1935.

time to time.<sup>15</sup> The most characteristic feature of these disturbances is their fluctuating and episodic nature and the fact that they may include a wide variety of neurologic and psychiatric disorders. This is well illustrated in the following case:

CASE 5 (this case will be reported in detail elsewhere<sup>16</sup>).—The patient was a 27 year old man with known Addison's disease of seven years' duration. Crisis first appeared during the development of thromboangiitis obliterans which involved both legs. Clinical and laboratory findings at that time were typical of Addison's disease. After this he was maintained in relatively good health, except during intercurrent infections, with an aqueous adrenal cortical extract, supplied by Drs. W. W. Swingle and L. G. Rowntree, and sodium chloride. One year before

TABLE 1.—*Neuropsychiatric Disturbances in Cases of Addison's Disease  
Recorded at the Mount Sinai Hospital, 1930-1940*

Case No.	Age, Yr.	Clinical Manifestations
18	35	Paresthesias of fingers and toes
19	50	Irregular pupils; diminished deep reflexes; diminished vibratory sense
20	50	Nervous; irritable; markedly uncooperative; depressed
21	57	Acute paranoid psychosis; noisy; difficult nursing problem; committed suicide after discharge
22	74	Confused; depressed; negativistic
23	53	Horner's syndrome; right abdominal reflexes depressed; bilateral suprapatellar and ankle clonus; hyperreflexia
24	38	Transient paresthesias of hands and feet; hyperactive deep reflexes; uncooperative patient
25	40	Transient amblyopia
26	42	Irregular pupils, reacting sluggishly; bilateral ptosis
27	23	Acute psychosis with delirium, disorientation, delusions, hallucinations and irrational, erotic behavior
11	23	Marked depression, with suicide attempt; uncooperative; childish
12	46	Personality change, with irritability, restlessness, depression and loss of interest; patient uncooperative, surly and complaining
13	22	Collapse, followed by appearance of spastic paraplegia, with hyperactive reflexes, clonus and spastic gait
14	47	Marked depression and agitation during impending crisis
5	27	Dyskinetic syndrome; convulsions; paresthesias; scotomas; marked personality change (see text)
16	54	Tearful, rambling, agitated, depressed, uncooperative; sensation of tightness and pulling in the hands; deep reflexes markedly depressed

admission the patient began to take the extract irregularly and finally discontinued it altogether. Within a few months he began to show a decided change in personality, with irritability, unmannerliness, deterioration of habits, unexplained bursts of anger and periods of amnesia and unreality. A dyskinetic syndrome, occasionally hemiballistic and occasionally choreoathetoid; trismic speech; ataxia;

15. Porter-Philips, J. G.: Nervous and Mental Symptoms in a Case of Addison's Disease, *Brit. M. J.* **2**:1705, 1912. Rushton, J. G.; Cragg, R. W., and Stalker, L. K.: Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands, *Arch. Int. Med.* **66**:531 (Sept.) 1940. Porot, M. A.: Psychose addisonienne; Essai de traitement chloruré, *Ann. méd. psychol.* **2**:665, 1937.

16. Engel, G. L., and Margolin, S.: Chronic Hypoglycemia in a Case of Addison's Disease, to be published. The patient in this case has already been the subject of two previous reports (Silbert, S.: Thromboangiitis Obliterans and Addison's Disease in the Same Patient, *J. A. M. A.* **108**:551 [Feb. 13] 1937. Rowntree, L. G.: Increasing Survival Time in Addison's Disease, *ibid.* **114**:2526 [June 29] 1940).

transient scotomas; patchy dysesthesias, and finally, convulsions made their appearance. All these manifestations showed striking fluctuation from time to time. The patient evinced a growing carbohydrate appetite, and his symptoms showed considerable variation with food habits, becoming worse after fasts. He was completely incapacitated by these symptoms and was admitted to the hospital May 3, 1940.

On physical examination the patient was well developed and well nourished, with striking pigmentation of the skin and mucous membranes. He moved about constantly in bed, showing jerky, involuntary movements of all his extremities. There were frequent twisting and arching movements of the trunk and grimaces of the face. Speech was markedly trisomic; the gait, broad based and ataxic. Marked finger to nose ataxia was present. The blood pressure was 135 systolic and 85 diastolic. The heart and lungs were normal. The left great toe had been amputated. Pulsations were absent in the left leg.

Examination of the blood revealed the hemoglobin content to be 17.5 Gm. per hundred cubic centimeters; the hematocrit reading, 48.5 per cent; the urea nitrogen, 21 mg. per hundred cubic centimeters; the sugar, 75 mg. per hundred cubic

TABLE 2.—*Dextrose Tolerance Tests, Case 5*

Date	Therapy	Blood Sugar, Mg./100 Ce.							Comment
		Fast- ing	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	4½ Hr.	
5/ 8	None.....	75	110	105	100	93	..	..	.....
5/22	Desoxycorticosterone acetate	85	125	100	85	105	..	..	.....
6/ 1	Aqueous adrenal cortical ex- tract (Upjohn).....	85	135	130	120	110	65	..	Reaction
7/19	Vitamin B complex.....	85	165	165	150	130	55	..	Reaction
7/20	Vitamin B complex and aqueous adrenal cortical extract (Upjohn).....	85	135	140	110	100	70	..	Reaction
3/ 5	Vitamin B complex and aqueous adrenal cortical extract (Upjohn).....	65	165	180	110	80	..	75	No reaction

centimeters; the chlorides, 95.6 milliequivalents per liter, and the sodium, 135.3 milliequivalents per liter.

Course: The patient was observed for a total of fourteen months. On admission it was found that he had a huge carbohydrate appetite, consuming an average of 800 Gm. of carbohydrate daily. Blood sugar values during the day ranged between 65 to 95 mg. per hundred cubic centimeters in spite of frequent feedings. Typical hypoglycemic reactions, characterized by profuse sweating, tachycardia, weakness and sudden personality change, were frequent and were associated with blood sugar levels of 45 to 75 mg. per hundred cubic centimeters. The dextrose tolerance curve on admission was flat (table 2). The patient's neuropsychiatric symptoms were transiently, but only partially, relieved by the frequent high carbohydrate feedings. Desoxycorticosterone acetate, which has little effect on carbohydrate metabolism in persons with Addison's disease,<sup>10b</sup> was ineffective. Definite and sustained improvement followed the use of an aqueous adrenal cortical extract (Upjohn) in a dose of 5 cc. daily. When, in addition to this, massive doses of thiamine hydrochloride (60 mg.), riboflavin (30 mg.) and nicotinamide (300 mg.) were used, an almost complete remission of the patient's presenting symptoms took place. He was able to return to normal activity and thereafter remained asymptomatic except during lapses in therapy and intercurrent infections. Associated with this clinical improvement were a decrease in daily carbohydrate intake to an average of 450 Gm. four times daily, a gain of 30 pounds (14 Kg.) in weight,

an increase in the height of the dextrose tolerance curve (table 2) and higher random levels of blood sugar (75 to 130 mg. per hundred cubic centimeters).

Electroencephalograms were taken at frequent intervals. The initial record (fig. 4) showed marked disorganization of the normal pattern, with much slow, irregular, high potential 2 to 6 per second activity. At this time it was not possible to influence this pattern more than slightly by large quantities of dextrose. As the patient's symptoms were brought under control and the carbohydrate utilization improved, the electroencephalogram showed progressive improvement. When the patient was asymptomatic, the record became normal, although the level of blood sugar at the time the record was taken was not significantly higher. Precipitation of a hypoglycemic reaction, with a fall of blood sugar to 70 mg. per hundred cubic centimeters, reproduced a record similar to the original one, but this record could now be restored to normal by the administration of dextrose.

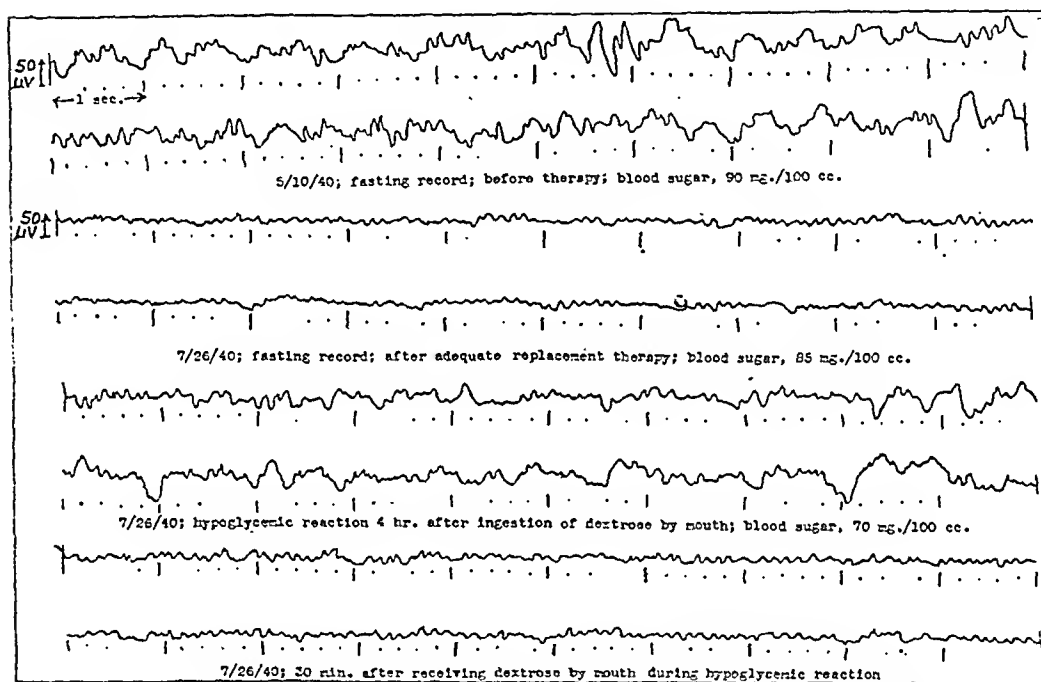


Fig. 4 (case 5).—Electroencephalograms made during the course of therapy of Addison's disease.

Comment: In this case striking neuropsychiatric symptoms were associated with a marked disturbance in carbohydrate metabolism and a diffuse abnormality in the electrical activity of the brain. The close parallel between the improvement in the clinical manifestations, the carbohydrate metabolism and the electroencephalographic activity on specific replacement therapy warrants the conclusion that they were intimately related. The electroencephalogram strongly resembles that reported for insulin hypoglycemia,<sup>6c</sup> but it is significant that in cases of induced hypoglycemia such records were obtained only with levels of blood sugar well under 50 mg. per hundred cubic centimeters and the records were promptly restored to normal by the administration of dextrose. The much higher levels of blood sugar in this case suggest

that the ability of the central nervous system to utilize the available sugar was also impaired. Even when the electroencephalogram had been restored to normal, a typical hypoglycemic record could be produced at a level of blood sugar of 70 mg. per hundred cubic centimeters, suggesting a lower threshold of cerebral reaction. A fuller discussion of the possible modes of action of the various therapeutic agents used in this case cannot be taken up here but will be the subject of another report.<sup>16a</sup>

In all cases of Addison's disease some degree of impairment of carbohydrate metabolism may be demonstrated. Cases in which it dominates the disease, however, are less commonly encountered, and the case just presented represents an unusually severe instance. Seven other cases of typical Addison's disease were studied. Four of these cases have been reported.<sup>17</sup> In all cases the patients were being treated with desoxycorticosterone acetate. Histories of 5 of the patients revealed significant neuropsychiatric disturbances (table 1).

Levels of sugar determined in blood drawn while the patients were fasting ranged from 50 to 95 mg. per hundred cubic centimeters. Dextrose tolerance tests are recorded in table 3. In 4 cases (15, 12, 13 and 17) the sugar tolerance curves were flat. In 3 cases (15, 14 and 12) the patients experienced hypoglycemic reactions four to five hours after receiving dextrose, sugar values at that time ranging from 55 to 65 mg. per hundred cubic centimeters. In 3 cases (11, 12 and 15) the patients gave histories suggestive of spontaneous hypoglycemic reactions.

Electroencephalograms taken under fasting conditions showed abnormalities in the spontaneous records in 5 cases. These consisted chiefly of bursts of 3 to 6 per second potentials, usually of higher voltage than the alpha waves and with no definite cortical focus (fig. 5). These waves could not immediately be influenced by dextrose but did show variation with the general condition of the patient. For example, the abnormalities in the record in case 11 (fig. 5) taken when the patient was exhibiting

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16a. Since this report was submitted for publication, it has been established that this patient is also suffering from a diffuse vascular disease. This has manifested itself by albuminuria, closure of retinal vessels, preretinal hemorrhages, mild hypertension (150 systolic and 100 diastolic) and recurrent indolent ulcers, biopsy of one of which revealed the vascular lesions. The relation between this condition and the Addisonian syndrome is entirely unclear at the present time. Therapy with adrenal cortical extract (Upjohn) was discontinued in October 1941, and again the patient appeared to be unaffected thereby for several months. However, he was readmitted to the hospital in June 1942, with recurrence of convulsions, loss of 10 pounds (5 Kg.) in weight and hypoglycemia. A dextrose tolerance curve on this admission was as follows: fasting, 70 mg. per hundred cubic centimeters; one hour, 80 mg.; two hours, 70 mg.; three hours, 50 mg., and four hours, 25 mg., with a marked reaction.

17. Soffer, L. J.; Engel, F. L., and Oppenheimer, B. S.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, *J. A. M. A.* **115**:1860 (Nov. 30) 1940.

TABLE 3.—*Dextrose Tolerance Curves and Electroencephalographic Abnormalities During Hyperventilation*

Case No.	Date	Diagnosis		Time After Dextrose Ingestion							
				Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	4 Hr.	5 Hr.	6 Hr.
11	7/ 9	Addison's disease....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG* Percentage of induction time.....	95 46 32	130 0 100	165 0 100	135 0 100	150 0 100	115 8 80	90 28 70	85 28 80
13	7/ 9	Addison's disease....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG. Percentage of induction time.....	90 58 30	105 1 99	105 23 70	70 60 26	85 53 25	85 53 26	90 63 30	90 43 25
15	8/23	Addison's disease....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG. Percentage of induction time.....	80 26 63	100 2 90	100 0 100	120 0 100	95 2 86	95 0 100	65 65 40	75 16 53
14	10/10	Addison's disease....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG. Percentage of induction time.....	85 7 53	135 0 100	145 0 100	130 0 100	90 0 100	55 10 45	80 0 100	75 0 100
16	3/12	Addison's disease....	Blood sugar, mg./100 cc.....	90	160	180	95	100			
12	10/25	Addison's disease....	Blood sugar, mg./100 cc.....	75	105	105	100	95	75	65	85
17	12/19	Addison's disease....	Blood sugar, mg./100 cc.....	90	105	100	85	80			
6	11/ 1	Ulcerative colitis.....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG. Percentage of induction time.....	85 40 43	100 0 100	105 0 100	95 0 100	75 4 72	65 10 66	75 2 90	
7	11/ 1	Anorexia nervosa....	Blood sugar, mg./100 cc..... Percentage of 2-5 per second waves, EEG. Percentage of induction time.....	85 26 63	110 0 100	110 0 100	100 3 86	80 25 90	65 52 52	70 37 74	70 25 88
8	9/ 5 10/ 9	Anorexia nervosa.... Anorexia nervosa....	Blood sugar, mg./100 cc..... Blood sugar, mg./100 cc.....	80 85	105 115	105 135	90 100	65 100	80 70	80	
9	11/25	Periarteritis nodosa	Blood sugar, mg./100 cc.....	90	105	120	95	65	70	80	
10	2/18	Anxiety state.....	Blood sugar, mg./100 cc.....	70	105	110	100	10	60	70	

\* The amount of the hyperventilation record made up of 2.5 per second waves, expressed as a percentage of the whole hyperventilation period.

† The length of time of hyperventilation before 2.5 per second waves appeared, expressed as a percentage of the whole time of hyperventilation. A value of 100 per cent. means no 2.5 per second waves appeared by the end of the hyperventilation period.



early evidences of insufficiency, including hypoglycemic episodes, disappeared completely several months later when her general condition and appetite were excellent.

The effects of hyperventilation on the electroencephalogram were studied in 6 cases (a preliminary report of this study has already been made<sup>18</sup>). In 5 of these the patients when fasting showed an abrupt appearance of long bursts of high potential (75 to 175 microvolts) waves, of a frequency of 2 to 5 per second, most often 2 to 3 per second. In some instances these bursts bore some resemblance to the wave and spike pattern of petit mal. The types of waves are illustrated in figure 6. The length of time of hyperventilation necessary to bring out these potentials was short, nineteen to fifty-eight seconds. This interval

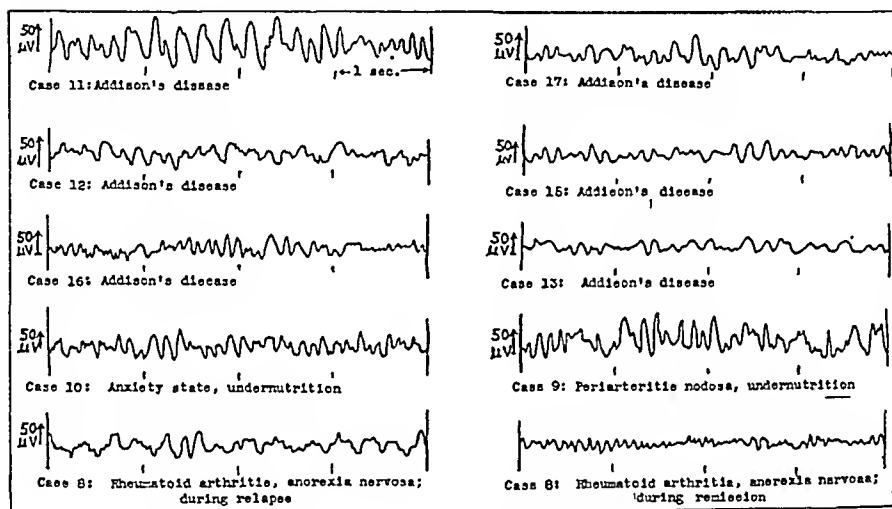


Fig. 5.—Spontaneous electroencephalographic abnormalities in cases of defective carbohydrate metabolism.

has been designated as the "induction time." After completion of ninety to one hundred and twenty seconds of hyperventilation repeated bursts of these high potential waves continued for varying periods up to four and a half minutes. This has been called the "after discharge."

This hyperventilation effect was found to be closely correlated with the level of blood sugar. Figure 7 shows a typical condensed hyperventilation record taken before and thirty minutes after the ingestion of sugar. Suppression of the slow potentials is complete, even after one hundred and twenty seconds of hyperventilation. In some instances

18. Engel, G. L., and Margolin, S.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, *Arch. Neurol. & Psychiat.* **45**:890 (May) 1941; Neuropsychiatric Disturbances in Addison's Disease and the Role of Impaired Carbohydrate Metabolism in Production of Abnormal Cerebral Function, *ibid.* **45**:881 (May) 1941.

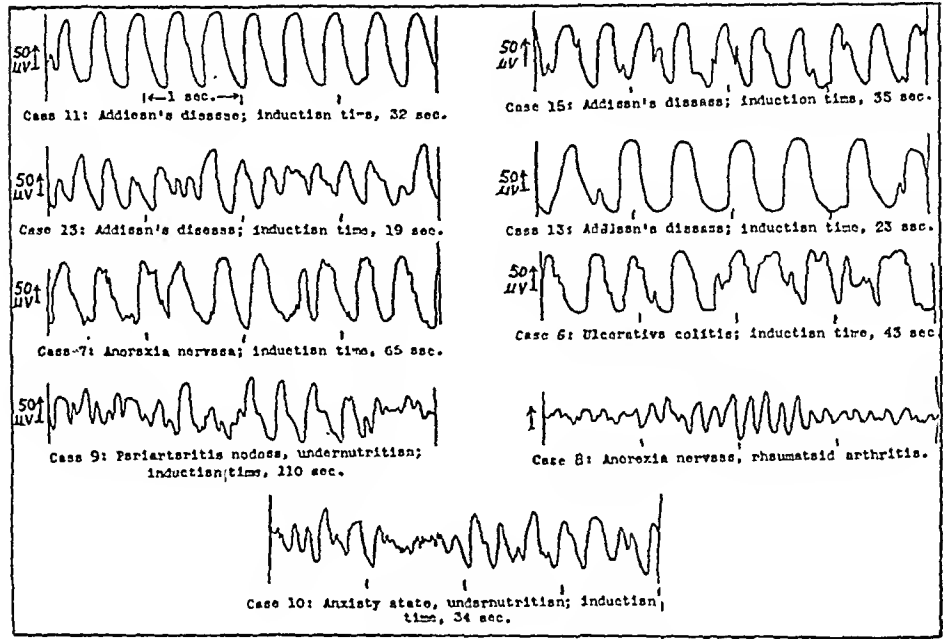


Fig. 6.—Types of waves appearing in electroencephalograms on hyperventilation in cases of defective carbohydrate metabolism.

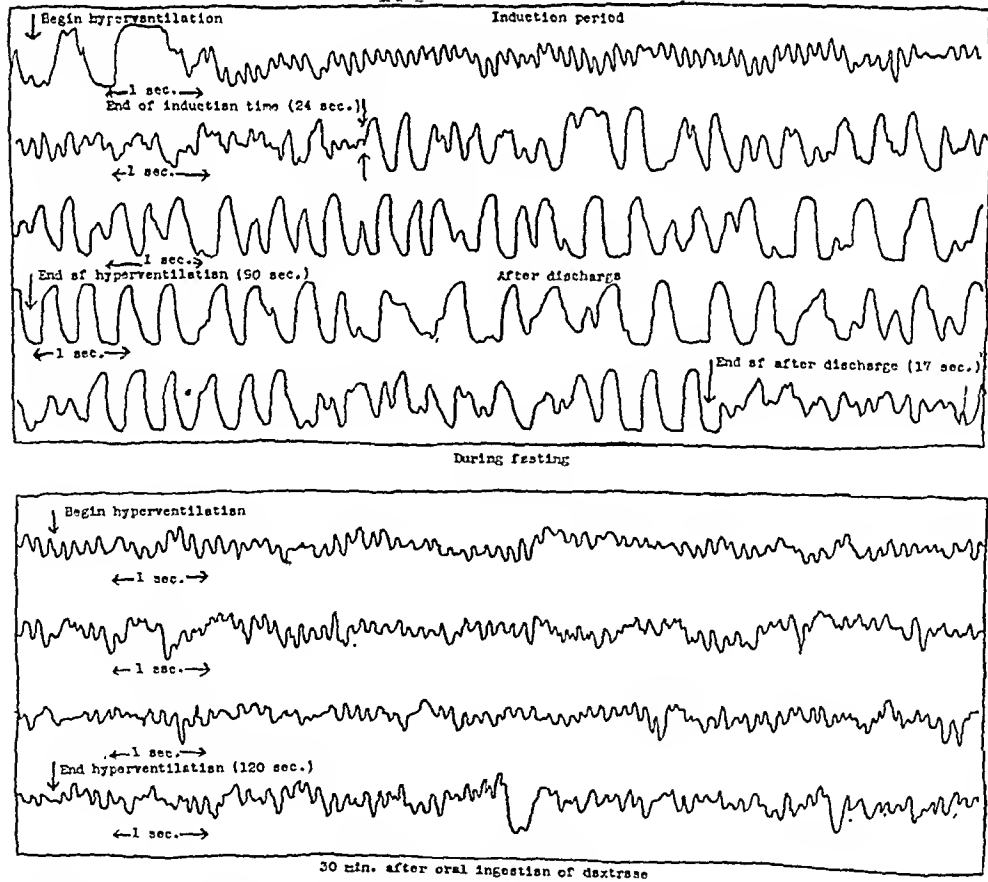


Fig. 7.—A typical hyperventilation record (condensed) in a case of Addison's disease before and thirty minutes after the ingestion of dextrose.

even four minutes of hyperventilation failed to bring out the slow waves after ingestion of sugar. When the amount of abnormal activity, expressed as the percentage of second intervals in the hyperventilation period containing 2 to 5 per second waves, was plotted against hourly levels of blood sugar, a close reciprocal relation was demonstrated (fig. 8, table 3). Similarly, the induction time, expressed in percentage of the hyperventilation time, paralleled the blood sugar curve. In other words, rising blood sugar decreased the amount of slow, high potential waves to the point of extinction, while the induction time was correspondingly increased. With a fall in blood sugar the reverse occurred. Dextrose appeared to protect the brain against the development of abnormal

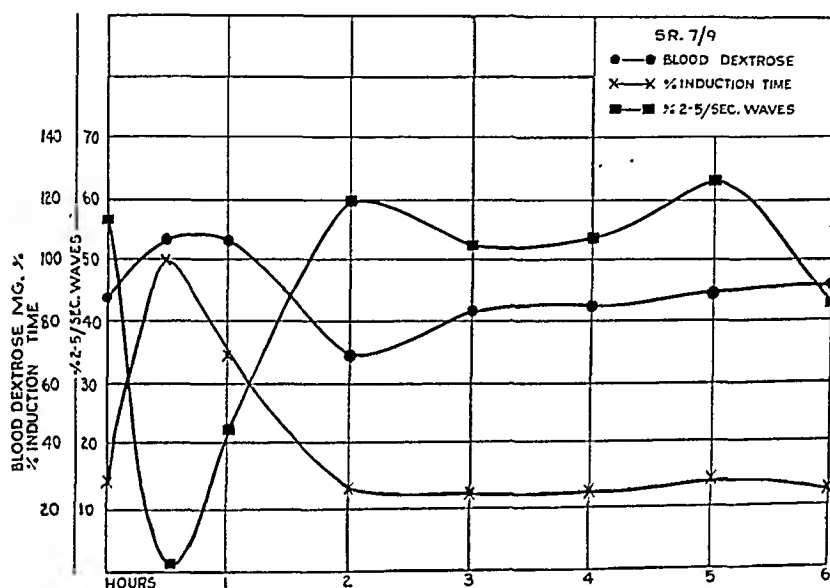


Fig. 8.—Relation between the level of blood sugar, the percentage of 2 to 5 per second waves and the percentage of induction time during a dextrose tolerance test in a patient with Addison's disease.

electrical activity. These observations were consistently checked in 11 experiments on 4 patients.

*Toxic Deficiency States.*—We observed 5 cases in which the patients had in common flat sugar tolerance curves, a tendency toward hypoglycemic reactions, neuropsychiatric disturbances and abnormal electroencephalograms. The underlying diseases varied widely, including 2 instances of anorexia nervosa, 1 with associated rheumatoid arthritis, and single instances of ulcerative colitis, periarteritis nodosa and anxiety state. All patients showed marked undernutrition and a relatively increased carbohydrate intake. No definite data are available as to the nature of the carbohydrate disturbance other than what might result from toxic, deficiency and nutritional factors.

In 2 cases (6 and 7) the patients had normal spontaneous electroencephalograms but showed marked hyperventilation effects identical

with those observed in cases of Addison's disease (figs. 6 and 7) except for slightly longer induction periods, ranging from forty-five to ninety seconds. After hyperventilation was discontinued, the abnormal slow potentials persisted for as long as ninety seconds. Abnormal potentials were abolished by dextrose and returned with falling blood sugar. In 1 case (6) four months after a complete recovery from active ulcerative colitis it was not possible to bring out any abnormal slow potentials, even after three minutes of hyperventilation in the fasting state. In the other case the patient showed no improvement clinically or electroencephalographically after two months of attempted therapy.

CASE 6.—H. B., a 26 year old man with typical ulcerative colitis of several years' duration, was readmitted to the hospital because of recurrence of diarrhea and fever and loss of 60 pounds (27 Kg.) of weight. He weighed 104 pounds (47 Kg.) and appeared acutely and chronically ill, undernourished and dehydrated. The tongue was red and sore. Cheiloses were present. The abdomen was scaphoid and diffusely tender. A perirectal abscess was present. The patient had a fever which ran a hectic course, lost weight steadily and had intractable diarrhea.

The neurologic examination revealed nothing abnormal. The patient constantly whined, complained and demanded attention. He had periods of sudden panic and uncontrollable outbursts of tears. The mood was frequently inappropriate. On one occasion he had sudden loss of consciousness lasting ten minutes. The patient evinced an excessive desire for sweets, which predominated in his limited diet.

The standard dextrose tolerance curve was flat (table 3).

After surgical intervention the patient made a dramatic recovery. When seen four months later, he weighed 160 pounds (73 Kg.), felt well and exhibited none of the abnormal trends noted during his acute illness. The electroencephalogram was now entirely normal.

CASE 7.—E. S., a 36 year old married white woman in a setting of emotional and domestic strain, experienced anorexia, nausea, vomiting, belching and episodes of epigastric pain, associated with loss of weight and strength. She became increasingly tense and irritable and had frequent crying spells. Menses became delayed.

On examination she appeared well developed but markedly undernourished and was complaining of abdominal distress. The blood pressure was 130 systolic and 90 diastolic. The abdomen was scaphoid and nontender. The pelvic examination revealed nothing abnormal.

Laboratory examination yielded the following data: hemoglobin concentration, 87 per cent; guaiac reaction of stool, negative; basal metabolic rate, —24 per cent; 15 mg. of urea nitrogen, 75 mg. of sugar, 540 mg. of cholesterol and 215 mg. of cholesterol ester per hundred cubic centimeters of blood, and dextrose tolerance curve, flat (table 3). Sigmoidoscopy and roentgen examination of the gastrointestinal tract revealed nothing abnormal.

The patient showed a great deal of anxiety and emotional lability and had crying spells and periods of agitation. She had frequent vague bodily complaints. Several episodes of extreme agitation, epigastric distress and sense of impending death responded promptly to a sweetened drink. The levels of blood sugar during these episodes ranged from 70 to 80 mg. per hundred cubic centimeters.

Attempts to improve the patient's nutrition were unsuccessful. It was felt that psychotherapy was indicated.

Comment: In this case the disturbed carbohydrate metabolism was secondary to the prolonged undernutrition. It appeared to increase the patient's abnormal trends and to make the development of insight into the nature of her gastrointestinal complaints more difficult.

In the 3 remaining cases the patients showed abnormalities in the electroencephalogram spontaneously and after hyperventilation. The hyperventilation effect was less striking in these cases. The spontaneous abnormalities again consisted of groups of slower (5 to 7 per second) waves. In 1 case (8) the patient had a marked remission of symptoms, during which the electroencephalogram became normal. With relapse the abnormal record again appeared (fig. 5).

CASE 8.—I. R., a 35 year old woman, experienced anorexia, weakness, pallor, loss of weight and amenorrhea fourteen months before admission, after serious emotional difficulties. Three months later psoriasis developed, followed by pain and stiffness of the joints and low grade fever. She had several admissions to other hospitals, where therapy was directed toward arthritis and anemia. Five months before entry she began to have episodes of weakness and faintness after fasts and had one convulsive episode. There was no past or family history of seizures. Her condition went gradually downhill, with a loss of 63 pounds (29 Kg.) of weight. Bronchopneumonia led to her final hospitalization.

The patient was markedly undernourished, cachectic and pale. Cheiloses were present, and the tongue and gums were red and sore. Numerous psoriatic patches were present. Most of the major joints, including those of the spine and phalanges, were stiff, painful, swollen and deformed. The blood pressure was 92 systolic and 68 diastolic. There were evidences of bronchopneumonia at the bases of both lungs. The abdomen was doughy. The neurologic examination revealed nothing abnormal.

The hemoglobin concentration was 72 per cent, and the blood contained 9 mg. of urea nitrogen, 70 mg. of sugar and 220 mg. of cholesterol per hundred cubic centimeters.

After a stormy course the patient recovered from the pneumonia. Severe involvement of the joints, fever, anorexia, weakness and faintness persisted. She frequently complained of dazed and unreal feelings, particularly before breakfast, and on one such occasion, she lost consciousness and convulsive movements developed. The level of blood sugar after the episode was 85 mg. per hundred cubic centimeters. The dextrose tolerance curve was flat (table 3). The electroencephalogram at this time showed the abnormalities illustrated in figures 5 and 6. The patient was markedly hyperirritable, emotionally labile, uncooperative and complaining and exhibited poor insight and judgment.

With the patient on a high calory, high vitamin diet and with spontaneous improvement in symptoms referable to the joints and a fall in temperature, appetite returned, episodes of morning weakness and faintness vanished and the general demeanor improved. The electroencephalogram was now entirely normal, before and after hyperventilation (figs. 5 and 6). The dextrose tolerance test showed some improvement (table 3).

Shortly after this the fever and symptoms referable to the joints recurred, and with them anorexia, weakness and the marked personality changes. The electroencephalogram again showed abnormal activity. The patient's course thereafter was progressively downhill, and she died four weeks later in collapse, after a generalized convulsion.

CASE 9.—E. G., a 19 year old girl, presented a one year history including rhinitis, asthma, diarrhea, pulmonary infiltrations, mononeuritides, eosinophilia, swelling of the joints and a maculopapulopurpuric eruption. Biopsy of affected skin confirmed the clinical diagnosis of periarteritis nodosa.

She was anorexic and extremely undernourished and showed marked emotional lability, with frequent weeping spells alternating with inappropriate hypomanic states and bursts of temper. Her family reported a change from her usual behavior.

The dextrose tolerance curve was flat (table 3). The electroencephalogram showed the abnormalities noted in figures 5 and 6. The hyperventilation effects vanished after the administration of sugar, remained in abeyance for two to three hours and then returned. The patient showed no improvement during the two and a half months of observation.

CASE 10.—P. D. was a 22 year old woman whose father had died of a massive hemoptysis. Eight months before admission she had a small hemoptysis, after which she became extremely upset and had frequent headaches, nervousness, weakness, vertigo, anorexia, palpitation and fatigue. Another hemoptysis led to her admission.

On examination she was tense and undernourished and was perspiring moderately. The blood pressure was 110 systolic and 80 diastolic. The remainder of the examination revealed nothing abnormal.

Extensive examination failed to reveal any cause for the hemoptysis, which was thought to be of benign bronchial origin.

A dextrose tolerance test yielded a flat curve, with a fall to 40 mg. per hundred cubic centimeters at three hours (table 3). The electroencephalogram showed bursts of 6 to 7 per second potentials and a shifting alpha frequency ranging from 8 to 12 per second. Hyperventilation produced bursts of 3 per second waves which disappeared for three hours after the ingestion of dextrose.

Comment on cases of abnormal carbohydrate metabolism: In this group of 13 cases we have attempted to demonstrate a relation between the neuropsychiatric symptoms and the altered carbohydrate metabolism. The electroencephalogram was used as an indicator of altered cerebral function. Two types of electrical abnormality were observed. First, there were spontaneous bursts of slow (2 to 6 per second) potentials, often of high voltage and originating diffusely from all portions of the cortex. These waves were only slightly influenced by changes in the level of blood sugar except during obvious hypoglycemic reactions, but they were unquestionably modified, to complete disappearance in some instances, by factors which effectively improved the carbohydrate metabolism, such as adequate replacement therapy in cases of Addison's disease or remission of the underlying disease in the other cases. An improvement in the dextrose tolerance curve always accompanied such clinical improvement. Secondly, the electroencephalograms in many cases showed an unusual sensitivity to the effects of hyperventilation. The sustained bursts of regular, high potential, slow waves, such as are illustrated, appeared after brief periods of overbreathing and persisted for long periods after overbreathing had been discontinued. This sensi-

tivity was markedly reduced by raising the blood sugar and in 1 instance, at least, disappeared completely when the underlying disease (ulcerative colitis) was cured. Whether this increased sensitivity to hyperventilation was due to a defect in the cerebrovascular mechanism which normally compensates for decreased carbon dioxide in the blood<sup>19</sup> or to a lowered threshold of cerebral reaction was not determined in this study, but it was unquestionably outside the normal range for the age group under consideration. The exceptionally high incidence of this phenomenon (5 out of 6) in a single group, such as the cases of Addison's disease, eliminated the possibility of mere coincidence. Further study of the incidence and mechanism of this phenomenon among various age groups will be necessary, however, before its clinical significance can be determined.

It is important to emphasize that the defect in carbohydrate metabolism in these cases involved more than simple hypoglycemia. Symptoms and electroencephalographic abnormalities were often present at relatively normal levels of blood sugar. When typical hypoglycemic reactions did occur, the level of blood sugar was usually higher than one ordinarily sees during induced insulin reactions in normal subjects. This also suggests a lowered threshold of cerebral reaction, possibly due to inefficient utilization of the available sugar by the central nervous system.

#### CONCLUSIONS

A series of cases has been presented in which clinical, metabolic and electroencephalographic data have been correlated. The results appear to warrant the conclusion that the varied neurologic and psychiatric manifestations observed could be attributed, on the one hand, to interference with the oxygen supply to the brain and, on the other, to inadequate carbohydrate utilization by the brain. The response to therapy directed toward correction of the underlying metabolic defect in several of these cases suggests the possibility of a more rational approach to the treatment of neurologic and psychiatric complications occurring in certain internal diseases. The value of the electroencephalograph in identifying this type of disturbance is clearly demonstrated and definitely suggests a more extensive use for this instrument in internal medicine.

#### SUMMARY

The requirements of the central nervous system for readily available oxygen and dextrose to maintain normal function form the basis for a report of a series of cases of generalized disease, in which neuro-

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19. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, *A. Research Nerv. & Ment. Dis., Proc.* (1937) **18**:277, 1938.

psychiatric symptoms were ascribable to disturbances in these factors. The electroencephalogram was used as an indicator of altered cerebral metabolism.

The effects of acute cerebral anemia were studied in 30 cases of hypersensitive carotid sinus reflex. In 22 cases the patients complained of episodes of weakness, dizziness, faintness or syncope, and in 8 they exhibited symptoms suggestive of focal disease of the central nervous system. In all cases the spontaneous symptoms were reproduced by stimulation of the carotid sinus and were accompanied by bursts of 3 to 6 per second waves in the electroencephalogram. Blocking the vagal response with atropine in the first group abolished the symptoms and electroencephalographic changes but was without influence in the second group.

Acute cerebral anoxemia was demonstrated in a case of congenital heart disease in which any cardioaccelerator stimulus resulted in marked tachycardia, dyspnea, cyanosis, faintness, syncope and convulsions. A simultaneous electroencephalogram yielded slow, irregular, high potential waves during the neurologic reaction produced by slight exertion.

Four cases of chronic cerebral anoxemia due to markedly impaired respiratory exchange in long-standing asthma, bronchitis and emphysema are presented. The progressive development of neuropsychiatric signs was accompanied by increased slowing and irregularity of the electroencephalogram.

The effects of disturbed carbohydrate metabolism were studied in 8 cases of Addison's disease and 5 cases of secondary toxic and deficiency factors. In all of these cases the patients showed a variety of neuropsychiatric manifestations, flat sugar tolerance curves, abnormal carbohydrate appetites and electroencephalographic changes. The last consisted of an unusual sensitivity to the effects of hyperventilation which was greatly influenced by changes in the level of blood sugar and of spontaneous bursts of abnormally slow waves. All the electroencephalographic changes appeared to be modifiable by factors which improved carbohydrate metabolism, such as adequate replacement therapy in cases of Addison's disease and remission or cure in the other cases. Clinical improvement went hand in hand with changes in carbohydrate metabolism and in the electroencephalogram.

The therapeutic implications of these observations are discussed.

Dr. Hans Strauss, electroencephalographer to the hospital, gave advice and aid in the interpretation of the electroencephalograms.

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# VASCULAR PHASE OF CHRONIC DIFFUSE GLOMERULONEPHRITIS

A CLINICOPATHOLOGIC STUDY

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The term "accelerated" arteriosclerosis was first suggested by Löhlein<sup>1</sup> to designate those vascular changes which differentiated the benign from the malignant form of nephrosclerosis. The concept of acceleration of the arteriosclerotic process was later supported by Klemperer and Otani.<sup>2</sup> The characteristic arterial alterations which they emphasized consisted of cellular proliferation of the intima of the larger interlobular and arcuate arteries with associated narrowing of the lumen and coexistent necrosis of the arteriolar walls. Since these investigators were also able to demonstrate the usual arteriosclerotic process of elastica lamellation, intimal fibrosis and arteriolar hyalinization, they expressed the opinion that the addition of cellular intimal proliferations and necrotizing lesions evidenced a more rapid, or "accelerated," development of arteriosclerosis. The acute vascular alterations were ascribed to an ischemic mechanism incident to the accelerated arteriosclerotic changes in the medium-sized arteries and were considered to be degenerative rather than inflammatory in nature.

It was also suggested that "accelerated" arteriosclerosis was not peculiar to essential hypertension alone but also appeared in renal diseases other than the primarily vascular variety. It was stated to occur notably in chronic diffuse glomerulonephritis, and the view was expressed by Klemperer and Otani<sup>2</sup> that in this condition, as in essential hypertension, the accelerated type of vascular lesion probably was of a similar

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From the Medical Services and Laboratories of Mount Sinai Hospital.

Presented in part at the Graduate Fortnight of the New York Academy of Medicine, "Medical and Surgical Disorders of the Urinary Tract," Nov. 1-12, 1937.

1. Löhlein, M.: Zur Pathogenese der vascularen Schrumpfnieren, *Med. Klin.* **12**:741, 1916; Ueber Schrumpfnieren, *Beitr. z. path. Anat. u. z. allg. Path.* **63**:570, 1917.

2. Klemperer, P., and Otani, S.: Malignant Nephrosclerosis (Fahr), *Arch. Path.* **11**:60 (Jan.) 1931.

morphogenesis. The inference further was drawn that in instances of chronic diffuse glomerulonephritis in which there was histologic evidence of "accelerated" arteriosclerosis a rapid tempo was exhibited clinically and therein the condition resembled malignant nephrosclerosis.

Fishberg<sup>3</sup> had previously called attention to the frequent occurrence of severe arteriosclerotic and arteriolonecrotic lesions in cases of chronic diffuse glomerulonephritis and expressed the opinion that such lesions were the result of hypertension. Kimmelstiel and Wilson<sup>4</sup> also noted the presence of "endarteritic" and arteriolonecrotic lesions in patients with chronic glomerulonephritis who had had severe hypertension. More recently Wagener and Keith<sup>5</sup> reported the coexistence of chronic diffuse glomerulonephritis and diffuse arteriolar disease and stated:

At present, the exact relationship between the two pathologic processes is unknown, and it is obvious that there is much still to learn regarding the etiology and development of the two conditions.

Baehr<sup>6</sup> and Wilson<sup>7</sup> have similarly alluded to the occurrence of advanced "malignant" arterial lesions in patients with chronic nephritis who exhibited severe hypertension, while especial emphasis was laid on the clinical resemblances of the conditions of these patients to malignant nephrosclerosis. The association of chronic diffuse glomerulonephritis and a clinical picture of malignant hypertension has been more recently reiterated by Derow and Altschule.<sup>8</sup>

The common appearance of the syndrome of "malignant" hypertension in cases of chronic diffuse glomerulonephritis has suggested that the morphologic substratum of the clinical resemblances may reside in the vascular lesions which are common to both morbid processes. It is the purpose of this report to present the results of a correlative study of this question.

#### MATERIAL AND METHOD

The material studied comprises 49 consecutive cases of chronic diffuse glomerulonephritis selected over twelve years (Jan. 1, 1927 to July 1, 1938) from a total of 5,232 autopsies. Specimens were fixed in a 40 per cent solution of formaldehyde U. S. P., Kaiserling I solution or Jores solution. Sections of the kidneys, pancreas,

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3. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, *Arch. Int. Med.* **40**:80 (July) 1927.

4. Kimmelstiel, P., and Wilson, C.: Benign and Malignant Hypertension and Nephrosclerosis, *Am. J. Path.* **12**:45, 1936.

5. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, *Medicine* **18**:317, 1939.

6. Baehr, G.: Clinical Pathological Conferences, Mount Sinai Hospital, *J. Mt. Sinai Hosp.* **3**:53, 1926; **5**:158, 1938.

7. Wilson, C., cited by Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, *Clin. Sc.* **3**:343, 1938.

8. Derow, H. A., and Altschule, M. O.: The Nature of Malignant Hypertension, *Ann. Int. Med.* **14**:1768, 1941.

adrenals, testes and myocardium in particular and all other available organs in addition were diligently examined. The sections were all embedded in paraffin and routinely stained with hematoxylin and eosin. The Weigert elastica-Van Gieson combination, the McGregor modification of the Mallory-Heidenhain and congo red stains were used where indicated.

In order to assure a purely objective evaluation of the histologic material, the study of the clinical aspects of the cases was postponed until the interpretation of morphologic data had been formulated. On the basis of the vascular picture a designation of either "slowly progressive" or "accelerated" type of arteriosclerosis was made. The criteria employed for the designation "advanced accelerated" form was extreme narrowing of the interlobular arteries produced by cellular intimal proliferation associated with necrosis of arterioles. In those instances of the accelerated type in which cellular intimal arterial proliferations were observed but arteriolonecrosis was absent the condition was termed "transitional." In the slowly progressive disease the changes included intimal thickening, fatty change, elastosis and arteriolar hyalinization.

A review of the clinical records was then made entirely separately. In each case the condition was similarly designated slowly progressive or accelerated ("malignant") on the basis of the height of hypertension and the presence or absence of neuroretinopathy. The anatomic and clinical data were then assembled and correlated (table 1).

A preliminary study was made not only of routine cases of acute and subacute diffuse glomerulonephritis but of various types of inflammatory processes, in order to ascertain the relation of inflammation to the vascular tree and to compare the arteriopathies with those observed in cases of the chronic phase of glomerulonephritis.

Deserving of special mention are the occasional cases in which differentiation between chronic diffuse glomerulonephritis and malignant nephrosclerosis was difficult due to widespread arterial changes. The extent of damage to the glomerular tufts and parenchyma and the age of the process constituted the basis for the final diagnosis. Wherever extensive active glomerular damage, replacement fibrosis and atrophy were observed, it was assumed that we were dealing with primary inflammatory glomerular disease. This belief was fortified by examining contracted benignly nephrosclerotic kidneys. In these, despite widespread vascular and glomerular involvement, the glomerular tufts still disclosed comparatively lesser changes than those in the nephritic group, while inflammatory lesions were absent. In cases of the malignant variety of essential hypertension active degenerative, inflammatory and proliferative glomerular lesions were observed, but these were usually isolated. To be sure, fibrotic loops or tufts were also encountered in cases of malignant nephrosclerosis, but these were of a more patchy character than those observed in cases of chronic diffuse glomerulonephritis. Criticism may be applied by the reader on the assumption that instances of malignant nephrosclerosis have been inadvertently included in our accelerated group. This possibility has been assiduously considered but, we believe, completely eliminated. All cases included in this study were considered to be unequivocal examples of diffuse glomerulonephritis.

## REPORTS OF THREE ILLUSTRATIVE CASES

### SLOWLY PROGRESSIVE TYPE

CASE 9.—S. G., a white female aged 44, entered Mount Sinai Hospital because of increasing weakness and malaise of three years' duration. Fourteen years previously she had had a spontaneous abortion. She had been well until the onset

TABLE 1.—Clinical Data in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis with Associated Arteriosclerosis

Case No.	Age, Yr.	Sex	Urea Nitrogen, Mg. per 100 Cc.	Cardiac Failure	Neuro-retino-pathy	Blood Pressure, Mm. Hg.		Weight of Kidneys, Gm.		Slowly Progressive Arteriosclerosis		Accelerated Arteriosclerosis		Arteriolonecrosis	
						Systolic	Diastolic	Right	Left	Kidneys	Other Organs	Kidneys	Other Organs	Kidneys	Other Organs
Slowly Progressive Arteriosclerosis															
1	36	M	135	+	0	160	100	120	110	++	++	0	0	0	0
2	23	M	82	-	0	126	90	130	130	+	+	0	0	0	0
3	24	M	242	+	0	163	104	60	60	+++	++	0	0	0	0
4	33	F	117	+	0	140	98	53	75	+++	++	0	0	0	0
5	24	M	269	-	0	160	96	60	Atrophic	+++	++	0	0	0	0
6	33	F	112	-	0	180	101	60	70	+++	++	0	0	0	0
7	22	F	66	+	0	134	80	70	Atrophic	++	0	0	0	0	0
8	15	M	238	+	0	100	60	75	75	Slight	0	0	0	0	0
9	44	F	120	+	0	175	100	150	150	+++	++	0	0	0	0
10	31	M	162	+	0	152	83	80	85	+++	++	0	0	0	0
11	52	F	160	-	0	128	78	105	120	++	+	0	0	0	0
12	42	F	144	-	0	140	74	100	130	+	0	0	0	0	0
13	2	M	90	-	No examination	138	100	130	140	+	Slight	0	0	0	0
14	52	M	162	+	0	210	100	130	140	+++	+	0	0	0	0
Transitional Accelerated Arteriosclerosis															
15	34	M	80	-	2	180	110	80	80	+++	+	Left, 0; right, +	0	0	0
16	30	F	158	-	0	192	130	50	120	++	++	++	0	0	0
17	22	F	136	-	1	218	134	45	50	++	Slight	++	0	0	0
18	23	F	181	+	2	208	92	70	70	++	0	++	0	0	0
19	13	F	195	-	2	140	100	60	60	+	+	++	0	0	0
20	18	M	180	-	0	152	102	60	60	++	++	++	0	0	0
21	41	F	145	+	0	230	120	85	100	++	++	Occasionally slight	0	0	0
22	21	M	88	+	No examination	193	130	160	160	++	++	+	0	0	0
23	48	M	138	+	No examination	210	110	110	110	++	++	+	0	0	0
24	54	M	85	+	2	225	112	200	200	+++	++	+	0	0	0
25	36	F	153	+	1	250	74	50	60	++	+	+	0	0	0
26	30	F	185	+	2	230	120	70	60	+++	++	++	0	0	0
27	21	M	164	+	1	160	100	125	135	+	+	+	0	0	0
Advanced Accelerated Arteriosclerosis															
28	35	F	76	+	1	224	120	70	50	++	++	+	+	+	0
29	24	M	169	-	1	190	44	100	125	+++	+	+++	0	0	0
30	22	F	184	-	1	170	120	75	75	+++	+	+++	0	0	0
31	28	F	131	+	2	220	180	50	60	+++	+	+	0	0	0
32	45	M	131	+	1	200	110	110	110	+++	+	+	0	0	0
33	27	M	120	+	2	216	152	110	110	+++	Slight	+	0	0	0
34	33	M	111	-	2	220	130	160	95	+++	Slight	+	0	0	0
35	37	F	154	+	1	224	110	130	120	+++	+	+	0	0	0
36	37	M	230	-	1	150	110	80	110	+++	+	+	0	0	0
37	20	F	118	+	2	200	140	75	75	++	+	Slight	0	0	0
38	42	M	120	+	1	180	98	115	130	++	+	+	0	0	0
39	48	M	110	+	1	214	136	100	100	++	+	+	0	0	0
40	21	M	228	+	2	220	140	110	95	++	+	+	0	0	0
41	36	M	153	+	2	216	136	40	40	+	0	+	0	0	0
42	28	F	142	+	1	230	160	125	125	+++	+	+	0	0	0
43	29	F	118	+	2	170	100	125	100	++	+	+	0	0	0
44	32	M	63	+	1	210	130	140	130	++	+	+	0	0	0
45	23	M	212	+	2	180	115	90	85	++	+	+	0	0	0
46	34	M	162	+	1	230	140	100	100	+++	+	+	0	0	0
47	24	M	195	-	1	220	130	130	130	++	+	+	0	0	0
48	25	M	124	-	2	246	160	75	Atrophic	++	+	+	+	+	+
49	22	M	169	+	2	220	140	110	100	++	+	+	+	+	+

\* The following figures have been employed with reference to the condition of the eyegrounds; 0, normal optic disks; 1, blurring of disk margins, and 2, measurable swelling of the nerve heads. Elsewhere in the table 0 signifies normal condition of an organ.

of her present complaints, when hypertension and albuminuria were first discovered. Postexertional dyspnea and palpitation soon became evident, while one year prior to her admission to the hospital she had begun to lose weight and to complain of generalized aches and pains. At that time she was examined in the outpatient department, where moderate albuminuria, inability to concentrate the urine above 1.010, a systolic blood pressure of 180 mm. of mercury, a diastolic pressure of 106 mm., a hemoglobin concentration of 54 per cent and a blood urea nitrogen content of 76 mg. per hundred cubic centimeters were observed. Two nights before hospitalization she had a bout of hemoptysis.

*Physical Examination.*—The patient was pallid and lethargic and her breath had a uriferous odor. Examination of the fundi revealed tortuous arteries; the optic disks showed no abnormalities. Numerous coarse rales were audible over the entire lower lobe of the right lung, and occasional rales were heard over the right side of the chest anteriorly. A systolic murmur was audible at the base of the heart, coarse over the pulmonic area and transmitted into the neck. The second aortic sound was greater than the second pulmonic sound. The cardiac rhythm was regular, with a rate of 100 per minute. There was no peripheral edema. The radial arteries were moderately sclerotic. The blood pressure was 175 systolic and 100 diastolic measured in millimeters of mercury.

*Laboratory Data.*—The hemoglobin concentration was 52 per cent (Sahli); the red cells numbered 2,850,000, and the white cells, 6,000 per cubic millimeter, with 71 per cent polymorphonuclear leukocytes. The Wassermann reaction of the blood was negative. A teleroentgenogram disclosed moderate enlargement of the heart both to the right and to the left. An electrocardiogram revealed low voltage and a tendency to left axis deviation. Urinalysis revealed a specific gravity varying between 1.008 and 1.014 and a positive reaction for albumin (2 plus), and occasional erythrocytes and casts were seen in the urinary sediment. The blood contained per hundred cubic centimeters an average of 120 mg. of urea nitrogen, 290 mg. of cholesterol, 8.0 mg. of creatinine and 525 mg. of chlorides. The carbon dioxide-combining power was 41 volumes per cent.

*Course of Illness.*—Despite the administration of intravenous fluids and supportive therapy, the patient died two weeks after her admission.

*Necropsy.*—The diagnoses included chronic diffuse glomerulonephritis with moderate contraction of the kidneys, hypertrophy and dilatation of the heart, early fibrinous pericarditis and pulmonary and cerebral edema. On gross examination the kidneys weighed 150 Gm. together and were normal in shape and moderately firm. The capsules were stripped with difficulty and revealed a finely granular surface with scattered hemorrhagic foci. The cut surfaces showed a pale brownish red, narrowed cortex through which irregular grayish yellow streaks were scattered. The corticomedullary demarcation was indistinct. The renal vasculature showed no significant gross abnormalities. The pelves and ureters and the urinary bladder presented no changes. Microscopic examination of the kidneys revealed widespread glomerular fibrosis, frequent adherence to the capsular epithelium and severe atrophy of the glomerular tufts. Glomerular ischemia was striking. Focal epithelial proliferation and an occasional increase in polymorphonuclear leukocytes were noted. The interstitial connective tissue was markedly increased. The renal vascular tree revealed slight to moderate elastic reduplication of the medium-sized or larger arteries with associated intimal thickening and narrowing of the lumens. There was moderate arteriolar thickening and early hyalinization. The tubules

were frequently dilated and contained granular and hyaline material, epithelial cells and leukocytes. The tubular cytoplasm was often granular, and a fair number of nuclei disclosed degenerative phenomena.

#### ACCELERATED TYPE

*Transitional Form.*—CASE 21.—S. L., a 41 year old housewife with known renal disease of twenty-two years' duration, entered Mount Sinai Hospital in the service of Dr. George Baelir on March 27, 1933 with a history of vomiting, weakness and pallor of two months' duration. She also complained of palpitation, urinary frequency and visual disturbances. Five days previously, a sore throat had developed and she had experienced considerable difficulty in swallowing. At this time her physician found enormously swollen tonsillar pillars. Three days later she expectorated small amounts of blood. On the day of hospitalization she again visited her physician, who discovered marked drowsiness and muscular twitchings. Her blood pressure was then 220 systolic and 120 diastolic, measured in millimeters of mercury. While she was in the physician's office she had a convulsion and then lapsed into coma. Phlebotomy reduced her blood pressure to 160 mm. of mercury systolic and 100 mm. diastolic.

**Physical Examination:** The patient was moribund, and her breath had a uriferous odor. Examination of the fundi revealed the margins of the optic disks to be sharp; the vessels were greatly narrowed and irregular, and few hemorrhages and some exudate were present. The heart was conspicuously enlarged. The cardiac rhythm was wholly irregular. The ventricular rate was 160 and the pulse rate 132 per minute. The second aortic sound was greater than the second pulmonic sound. The edge of the liver was palpable 2 fingerbreadths below the costal margin. Slight edema of the lower extremities was present. The blood pressure was now 180 mm. of mercury systolic and 120 mm. diastolic.

**Laboratory Data:** The hemoglobin concentration was 55 per cent (Sahli), and the white cell count, 9,100 per cubic millimeter, with 95 per cent polymorphonuclear leukocytes. Urinalysis revealed a specific gravity of 1.008 and a positive reaction for albumin (3 plus), and occasional red cells and frequent white cells were seen in the sediment. The blood contained 145 mg. of nitrogen and 170 mg. of sugar per hundred cubic centimeters. The carbon dioxide-combining power was 26.5 volumes per cent.

**Course of Illness:** The patient suffered a convulsion shortly after admission. Accordingly, a lumbar tap was performed, which showed a slightly increased spinal fluid pressure. The tap was soon followed by another convulsion and death.

**Necropsy:** The diagnoses included chronic diffuse glomerulonephritis with moderate contraction of the kidneys, hypertrophy and dilatation of all chambers of the heart, acute fibrinous pericarditis, pulmonary edema, chronic passive congestion of the lungs and the liver and bronchopneumonia of the lower lobes of the lungs. Death was attributed to the association of renal and of cardiac failure. On gross examination the kidneys were small; the right one weighed 85 Gm., and the left one, 100 Gm. The capsules were stripped with considerable difficulty, leaving a pale gray, finely granular surface. The granules were pinhead to split pea in size, and the intervening tissue was smooth and slightly depressed. On section the cortex was diminished in width, and the basic markings were absent; the corticomedullary demarcation was indistinct. Microscopic examination of the kidneys revealed widespread partial to complete replacement fibrosis, atrophy and focal and confluent hyalinization of the malpighian bodies. A fair number were conspicuously enlarged, contained increased numbers of epithelial and endothelial cells and were irregularly

adherent to the capsular epithelium. The interstitium was irregularly increased and was the site of small round cells, plasma cells and fibroblasts. There was a moderate degree of collar-like alteration around the bodies; their lumens were commonly distorted, occasionally dilated and showing cellular multiplication, but more frequently compressed with cellular atrophy. The lumens contained epithelial, red and rarely white cells and albuminous and hyaline material. Peritubular hyalinization and marked capillary engorgement were noted. There was also evidence of associated acute and subacute pyelonephritis. Cellular and edematous thickening of the larger, medium-sized and smaller interlobular arteries with occasional severe narrowing of the lumens was striking. Scattered mural calcification of the medium-sized arteries was noted. Occasional medial hypertrophy, hyalinization of the arteriolar walls and fibrotic intimal thickening of the larger arteries were also encountered. No necrotic vascular lesions were present.

*Advanced Form.*—CASE 33.—First Admission: R. K., a 27 year old Hungarian clerk, had been well until six years prior to his admission to Mount Sinai Hospital in the service of Dr. B. S. Oppenheimer on May 11, 1931, when he first noticed edema of both legs. He was then hospitalized at another institution, where a diagnosis of acute diffuse glomerular nephritis was made. At that time the blood contained 20 mg. of urea nitrogen per hundred cubic centimeters. He was discharged improved after sixteen days and remained asymptomatic for six years. Four weeks before his admission to Mount Sinai Hospital, his ankles and legs again began to swell and he complained of marked weakness and oliguria. Six days previously he had noted hematuria.

Physical examination: The patient had a pasty complexion and a puffy face. The optic nerve heads were of good color; the margins were slightly serrated. The retinal arteries showed a high light reflex and evidence of perivascularitis. The neck veins were full. Dulness was elicited at the bases of both lungs. There was no clinical evidence of cardiac enlargement or no cardiac murmurs. The second pulmonary sound was greater than the second aortic sound. A fluid wave was elicited in the abdomen, and pitting edema was present over the ankles and the trunk. The blood pressure was 200 systolic and 110 diastolic, measured in millimeters of mercury.

Laboratory data: The hemoglobin concentration was 65 per cent (Sahli). The white cells numbered 6,400 per cubic millimeter, with 80 per cent polymorphonuclear leukocytes. Urinalysis revealed a specific gravity not exceeding 1.012 and a positive reaction for albumin (4 plus); many erythrocytes and occasional casts were seen in the sediment. The result of the Esbach determination was 7 Gm. daily. The blood contained per hundred cubic centimeters 66 mg. of urea nitrogen, 270 mg. of cholesterol, 7.2 mg. of calcium, 3.7 mg. of phosphorus and 4.1 Gm. of total protein, with 2.3 Gm. of albumin and 1.8 Gm. of globulin. The carbon dioxide-combining power was 41 volumes per cent. An electrocardiogram showed changes suggestive of left ventricular preponderance; a teleroentgenogram showed an enlarged heart. The diagnosis was chronic diffuse glomerulonephritis in an early nephrotic phase.

Course of illness: The patient was treated with dietary means and injections of mercurials. He was discharged six weeks after this admission, at which time the urea nitrogen in the blood had fallen to 38 mg. per hundred cubic centimeters. Erythrocytes were no longer seen in the urinary sediment, and the result of the Esbach determination fell to 2 Gm. for twenty-four hours. The edema of the ankles was then minimal.

Second Admission: The patient was readmitted seven months later because of blurred vision, headaches, expectoration of rusty sputum, vomiting and loss of

20 pounds (9 Kg.) in weight. Two months prior to readmission he was seen at the follow-up clinic, where blurring of the margins of the optic disks was noted. Evidence of moderate cardiac failure was present. His blood pressure at that time was 170 systolic and 110 diastolic, measured in millimeters of mercury. On admission to the hospital his blood pressure was 230 systolic and 120 diastolic. The optic nerve heads were now edematous, and their margins, blurred and hyperemic. The retinal arteries were thin and of irregular caliber. A large amount of exudate was present. There were a star-shaped figure at the macula and zones of fibrinous exudate about the nerve heads. Auscultation of the chest disclosed a gallop cardiac rhythm and rales throughout the lungs. There was slight pretibial edema.

Laboratory data: The urine concentration test showed a maximum concentration to 1.012. The reaction for albumin was positive (2 plus). Neither casts nor erythrocytes were found in the sediment. The blood contained per hundred cubic centimeters 57 mg. of urea nitrogen, 4 mg. of creatinine, 7.4 mg. of calcium, 4.4 mg. of phosphorus, 340 mg. of cholesterol and 5.5 Gm. of total protein. An electrocardiogram again showed deviation of the electrical axis to the left, and the T wave in lead II was partially inverted. A teleroentgenogram revealed evidence of dilatation of both ventricles. The patient remained in the hospital for seven days, with little change in his condition, and left the hospital against advice.

Third Admission: Two months later the patient again sought admission because of severe epistaxis. The previous symptoms had become progressively worse.

Physical examination: The optic nerve heads and margins of the optic disks were obscured. There was slight peripapillary edema (1 D.). The edge of the liver was palpable at the level of the umbilicus, and both legs were edematous. The blood pressure was 216 systolic and 152 diastolic, measured in millimeters of mercury.

Laboratory data: The specific gravity of the urine was 1.010. Albuminuria and cylindruria were present.

Course of illness: The blood contained 68 mg. of urea nitrogen per hundred cubic centimeters, but the level rose progressively in ten days to 120 mg. per hundred cubic centimeters. The daily urinary output fell to 300 cc. Treatment of cardiac failure was of no avail, and the patient died with the typical manifestations of uremia (urea frost, muscular twitchings and a pericardial friction rub).

Necropsy: The diagnoses included chronic diffuse glomerulonephritis with vascular necrosis, marked fibrinous pericarditis, hypertrophy and dilatation of left cardiac and right ventricular chambers, coronary arteriosclerosis with moderate narrowing of the lumens, chronic passive congestion of all viscera and anasarca. Death was due to the association of renal and of cardiac failure. On gross examination each kidney weighed 110 Gm. and was firm in consistency. The capsules stripped with moderate ease, revealing a diffusely granular, reddish gray surface with scattered, discrete, pinhead-sized hemorrhages. The granules varied from 1 to 2 mm. in diameter and were enclosed by depressed reddish gray zones. The sectioned surfaces disclosed sharp corticomedullary delineation. The pelves and ureters and the urinary bladder were the seat of a few submucosal hemorrhages. On histologic examination there was a paucity of glomeruli. The majority showed various stages of fibrosis, atrophy and hyalinization, while scattered tufts revealed increased cellularity with predominant epithelial cell proliferation and here and there hyperplasia of the capsular epithelium with suggestive early crescent formation. Adhesion between the tufts and capsule, interstitial fibrosis with conspicuous infiltration with lymphocytes and scattered foci of hemorrhage were noted. The tubular epithelium showed degenerative alterations, including fatty change, nuclear pyknosis and irregularly alternating dilatation and compression of



the lumens. The lumens frequently contained abundant numbers of erythrocytes, eosinophilic debris and desquamated epithelial cells. In addition to intimal fibrosis, elastosis and arteriohyalinization, there were cellular and edematous intimal thickening of the medium-sized arteries, fatty change, "hyaline" thrombi of arterioles, scattered arteriolonecrosis and impregnation of their walls with erythrocytes. Of the other organs only the pancreas and adrenals showed any significant vascular alterations. These consisted of "foamy" and cellular intimal thickening with associated narrowing of the lumen, arteriohyalinization of the pancreatic arteries and hyaline intimal degeneration of scattered adrenal arterioles.

### CLINICAL FINDINGS (Table 1)

A preponderant number of males were affected in the advanced accelerated group, while the remaining groups showed no significant sex variations. The age range extended from 2 to 60 years. The average duration of the clinical picture of glomerulonephritis was approximately similar in all groups, although the exact onset of the

TABLE 2.—*Range of Blood Pressure in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis*

Type of Arteriosclerosis	Systolic Pressure		Diastolic Pressure	
	200 Mm. Hg or Over, %	Below 160 Mm. Hg %	120 Mm. Hg or Over, %	100 Mm. Hg or Over, %
Slowly progressive.....	7 (1 case)	80	0	30
Accelerated				
Transitional.....	54	16	38	84
Advanced.....	73	4 (1 case)	70	91

disease in several instances could not be accurately ascertained. However, with the appearance of severe hypertension the course of a patient's illness was more rapidly terminated.

Albumin, erythrocytes, all forms of casts and leukocytes in varying numbers were present in the urine in all cases. No correlation could be established between either the severity or the tempo of the clinical course and the character of the urinary sediment. Poor variability of the specific gravity of the urine and azotemia were found to be common to all cases. In the greater number death was attributable to uremia alone, while in some cases the association either of cardiac failure, an intercurrent infection or a surgical procedure was considered to be a responsible factor. Cardiac failure was found to be a more frequent complication in the accelerated group. In those cases in which definite cardiac insufficiency was present, it was believed to have either precipitated or intensified the uremic manifestations through the mechanism of prerenal fluid deviation.

The blood pressure in the three groups exhibited striking differences (tables 1 and 2). The systolic blood pressure in the slowly progressive group usually varied between 100 and 180 mm. of mercury. In 1

instance it was found to be 210 mm. In 80 per cent of the cases, however, it was below 160 mm. The diastolic blood pressure ranged between 60 and 104 mm., while in only 2 cases did it exceed 100 mm. It is worthy of emphasis that the blood pressure in 5 instances was normal despite the absence of cardiac failure. Similar observations of normal blood pressure in patients with glomerulonephritis have been reported by Jores<sup>9</sup> and others.<sup>10</sup>

In contrast to the systolic blood pressure in the slowly progressive group, that in the advanced accelerated group varied between 150 and 246 mm. of mercury. In 73 per cent of cases the systolic blood pressure was 200 mm. or higher, while in only 1 case was it below 160 mm. The diastolic blood pressure level in 91 per cent had been 100 mm. of mercury or higher, and in 70 per cent it had reached 120 mm. or more. In the transitional group the systolic blood pressure varied between 140 and 280 mm. of mercury. In 54 per cent of cases the systolic blood pressure had exceeded 200 mm. In 2 cases it was below 160 mm.; the patient in 1 case was a boy aged 13 and in the other an infant aged 2. In 84 per cent of the cases in the transitional group the diastolic blood pressure reached 100 mm. of mercury or over and in 38 per cent it was 120 mm. of mercury or higher. Thus a striking association of severe vascular lesions with marked hypertension was noted to exist.

The fundus oculi both in the advanced accelerated and in the transitional group showed conspicuous differences from that in the cases of slowly progressive disease, although narrow vessels and ones of irregular caliber, arteriovenous compression and retinal exudates were common to all cases included in this study. The optic disks were normal in every case in the slowly progressive group, while neuroretinopathy was observed in 96 per cent of the cases in the advanced accelerated group (tables 1 and 3). Papilledema was likewise noted in 62 per cent of the cases in the transitional group. It is significant that whereas normal optic disks were visualized in 3 cases during earlier periods of hospitalization, papilledema was seen to have appeared in the same cases during subsequent observations. In 2 other cases atrophy had replaced edema of the nerve head. Peripapillary retinal edema was present in 14 instances. In 1 case the optic disk of one eye was normal, while the other showed definite swelling, presumably consequent to unilateral vascular involvement. Detachment of the retina secondary to the underlying edema had occurred in 2 patients, while reattachment was observed

9. Jores, L.: Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie von pathologische Standpunkt, *Deutsches Arch. f. klin. Med.* **94**:1, 1908.

10. Foster, N. B.: The Relations of Hypertension to Cardiorenal Diseases, *Am. J. M. Sc.* **164**:808, 1922. Bannick, E. G.: Severe Chronic Glomerular Nephritis Without Hypertension, Cardiac Hypertrophy or Retinal Changes: Report of Two Cases, *Arch. Int. Med.* **39**:741 (May) 1927.

to have taken place in 1. In only 4 instances in the advanced accelerated and transitional groups were the optic nerve heads considered to be normal in appearance—1 in the former and 3 in the latter. In 3 cases the fundi were not described.

The color of the disks was definitely recorded in 13 of the 32 cases in which neuroretinopathy had been present. In 8 hyperemia of the disk was observed, while in 5 the nerve heads were pale. Thus, in our cases hyperemia of the disk was noted with greater frequency than was pallor.

These data are somewhat at variance with those reported by Keith and his co-workers,<sup>11</sup> who stressed pallor as characteristic of the disk in patients with glomerulonephritis and held this in contrast to hyperemia of the disk occurring in cases of malignant nephrosclerosis. They expressed the belief, in addition, that sclerosis of the retinal arterioles was absent in cases of chronic diffuse glomerulonephritis. In our series, however, retinal arteriosclerosis had been observed in almost every case.

TABLE 3.—Incidence of Neuroretinopathy in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis

Type of Arteriosclerosis	Percentage of Cases
Slowly progressive.....	0
Accelerated	
Transitional.....	62
Advanced.....	96

A similar experience had been previously stated by Cannady and O'Hare.<sup>12</sup>

FACTORS CONCERNED IN OCCURRENCE OF OCULAR LESIONS

It appeared in this study that when severe hypertension had become definitely established, advanced neuroretinopathy either was coexistent or was soon to follow and, further, that it indicated the probable existence of accelerated visceral vascular lesions. The belief that the neuroretinopathic changes were the sequel of long-standing severe hypertension was substantiated further by their absence in the slowly progressive group and their development in those instances in which there had been a pronounced elevation of blood pressure. Moschowitz<sup>13</sup> long ago intimated that such retinopathy is secondary to arterial lesions, which themselves represent the effects of a preexistent hypertension.

11. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.  
12. Cannady, E. W., and O'Hare, J. P.: A Critical Survey of the Retinal Lesions in Chronic Glomerular Nephritis, J. A. M. A. **103**:6 (July 7) 1934.  
13. Moschowitz, E.: Hypertension with Minimal Renal Lesions, J. A. M. A. **77**:1095 (Oct. 1) 1921.

The studies reported by Cannady and O'Hare<sup>12</sup> lend support to this belief. In the series of cases of chronic diffuse glomerulonephritis which they investigated, severe retinal lesions were noted in 25 of 32 cases. Hypertension was found to precede the appearance of retinal arteriolar change in 13 of the 17 cases in which these authors had observed the disease since its early stages. It is noteworthy that in 2 of their cases in which retinal lesions were absent hypertension was also not present.

The parallelism which existed between extreme hypertension and neuroretinitis in cases of chronic diffuse glomerulonephritis was fully recognized by Fishberg and Oppenheimer.<sup>14</sup> Of 45 patients with chronic diffuse glomerulonephritis, 17 exhibited neuroretinitis, and "all of these patients gave evidence of either present or past hypertension." After reviewing the evidence, Fishberg<sup>15</sup> subsequently concluded: "Hypertensive neuroretinopathy appears to be of the same pathogenesis in both essential hypertension and glomerulonephritis."

In view of the presence of azotemia in the cases presented here, such a fact may be judged erroneously to play a contributory role in the appearance of the neuroretinopathic picture. Several studies, however, deny importance to this contention. Behan<sup>16</sup> recorded the presence of neuroretinitis in patients with hypertension in whom evidence of renal impairment was absent. The observations of Benedict<sup>17</sup> and others<sup>18</sup> of the absence of azotemia in patients who exhibited neuroretinitis similarly militate against the assumption that azotemia is in any way responsible for the appearance of this picture. Of interest in this connection is the fact that uremia due to various causes may be present for long periods without the coexistence of retinal lesions.<sup>14</sup> These views are firmly borne out by the absence of neuroretinitis in our cases of slowly progressive arteriosclerosis despite the existence of long-standing azotemia.

An additional point worthy of comment is the possible differential diagnostic value of neuroretinopathy in instances of hypertension. Keith, Wagener and Kernohan<sup>11</sup> originally averred that a clinical differentiation between chronic diffuse glomerulonephritis and malignant

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14. Fishberg, A. M., and Oppenheimer, B. S.: The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Diseases, *Arch. Int. Med.* **46**:901 (Dec.) 1930.

15. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 4, Philadelphia, Lea & Febiger, 1939.

16. Behan, J. L.: The Fundus Changes in Nephritis, *J. A. M. A.* **78**:1691 (June 3) 1922.

17. Benedict, W. L.: Retinitis Associated with Disease of the Cardiovascular System, *New York M. J.* **117**:741, 1923.

18. (a) Volhard, F.: Ueber die Retinitis Albuminurica, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **33**:422, 1921. (b) Wagener, H. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *Arch. Int. Med.* **34**:374 (Sept.) 1924. (c) Fishberg.<sup>15</sup>

hypertensive vascular disease might be made ophthalmoscopically on the basis of the color of the disk, the presence of arteriosclerosis, the extent of retinal edema and types of exudate. However, the criteria proposed by these authors were not applicable in many of our cases. Furthermore, the malignant neuroretinopathic picture has been found to exist not in these entities alone but in other diseases in which severe hypertension supervenes. Longcope,<sup>19</sup> for example, has observed a striking relation between arteriolar lesions of the fundus—"hemorrhagic retinitis"—and hypertension in instances of pyelonephritis. Moreover, the occurrence of neuroretinitis in cases of neoplasm of an adrenal, polyarteritis nodosa, polycystic kidneys and even renal amyloidosis in which severe hypertension supervenes is well known. Accordingly, the supposed differential diagnostic importance of the retinal findings would appear to be nullified. Cannady and O'Hare,<sup>12</sup> Baehr<sup>6</sup> and Fishberg<sup>15</sup> have similarly negated the possibility of differentiation in most cases of hypertension on the basis of the ophthalmoscopic picture alone.

It is worthy of reemphasis that the neuroretinopathy of hypertensive patients is in no way induced by the azotemia but is rather the expression of an increased intracranial pressure<sup>20</sup> or is incident to the occurrence of ocular vascular lesions and should be viewed as evidence of the accelerated or malignant phase of hypertension no matter what its basic cause might be. It appears more accurate, then, to refer to the full development of this clinical picture in which severe hypertension and papilledema exist as the syndrome of "malignant hypertension"<sup>18b</sup> possibly associated with accelerated arteriosclerosis, and the presence of all disease entities which are capable of producing this clinical picture should be duly suspected.

#### PATHOLOGIC VASCULAR CHANGES

The vascular pictures of the three groups presented striking histologic differences.

*Slowly Progressive, or "Negative," Type.*—The vascular lesions in the first group consisted of slight to occasionally severe intimal thickening of the interlobular arteries with associated narrowing of their lumens. The thickening was callus in type, with only here and there a fibroblast or two. The focal cellular change was noted only within the intima of the larger arteries and because of its sparsity was believed to convey no significance. Kimmelstiel and Wilson<sup>4</sup> considered limited cellular pro-

19. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, *Ann. Int. Med.* **11**:149, 1937.

20. Kessler, M. M.; Moschowitz, E., and Savitsky, L.: The Hematoencephalic Barrier: The Study of the Clinical Aspects and the Mechanism of the Development of Hypertension of the Cerebrospinal Fluid in Hypertensive Disease, *J. Nerv. & Ment. Dis.* **90**:594, 1939. Fishberg.<sup>15</sup>

liferations of this variety to be related to a severe degree of renal contraction. Fat deposition was noted often within the intimal layer, but hypertrophy of the medial layer was only occasionally encountered. In sections showing fibrous intimal thickening of any considerable degree medial atrophy was invariably associated.

In the main, the larger arteries showed slight to moderate hyperplasia of the internal elastic membrane and frequent fibrillar disruption, while the arterioles, including the vasa afferentia, revealed hyalinized walls and fatty change with concomitant encroachment on the lumen. In a few cases the vascular tree disclosed minimal lesions (table 1).

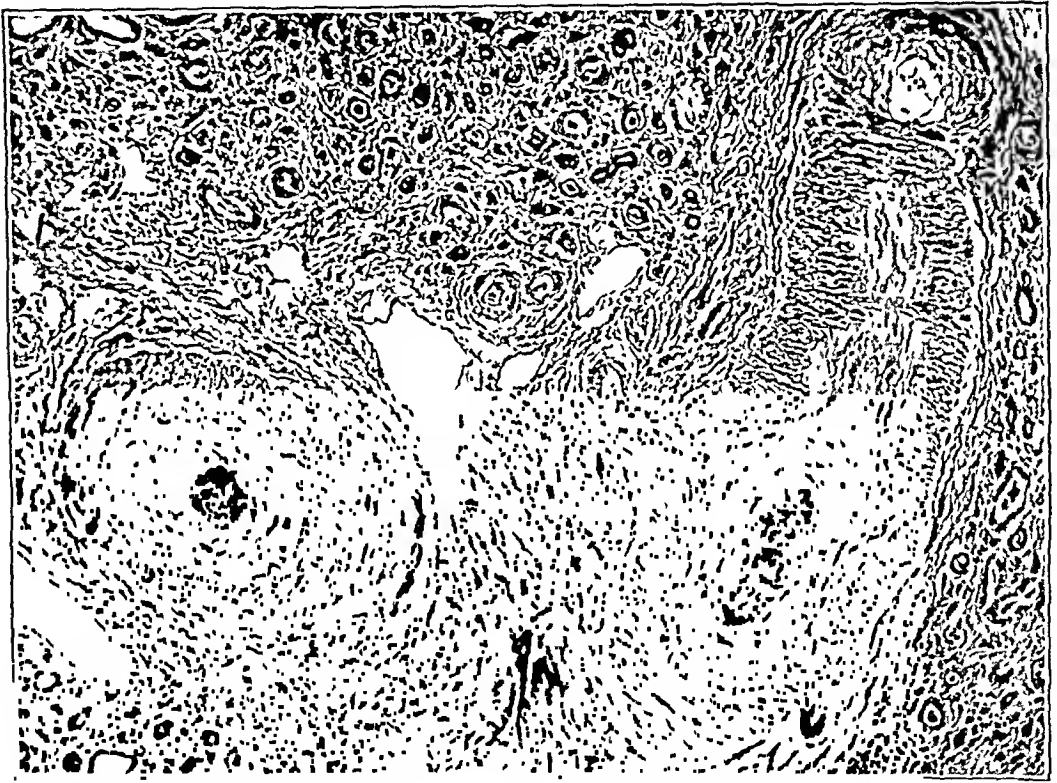


Fig. 1.—Photomicrograph ( $\times 77$ ) of an interlobular artery showing cellular proliferation and the looseness of the intimal layer.

*Accelerated Type.—Transitional Form:* This group comprises those instances in which cellular proliferation within the intimal layers of the interlobular arteries was disclosed, in addition to the alterations just outlined (fig. 1). The intimal cells were of the type noted by Klemperer and Otani,<sup>2</sup> i. e., "fibroblasts, which often show a reticulated arrangement, and mononuclear cells with a large amount of fat (foam cells)." Occasionally, an abundant cellular and delicate fibrillar proliferation was found in the intima of the larger arteries, with associated narrowing of the lumen (figs. 2 and 3). Scattered mural foci of calcification were present occasionally, in the smaller branches. No case in which arteriolonecrosis was present was included in this group.



Fig. 2.—Photomicrograph ( $\times 136$ ) of medium-sized arteries with cellularity of the intima.

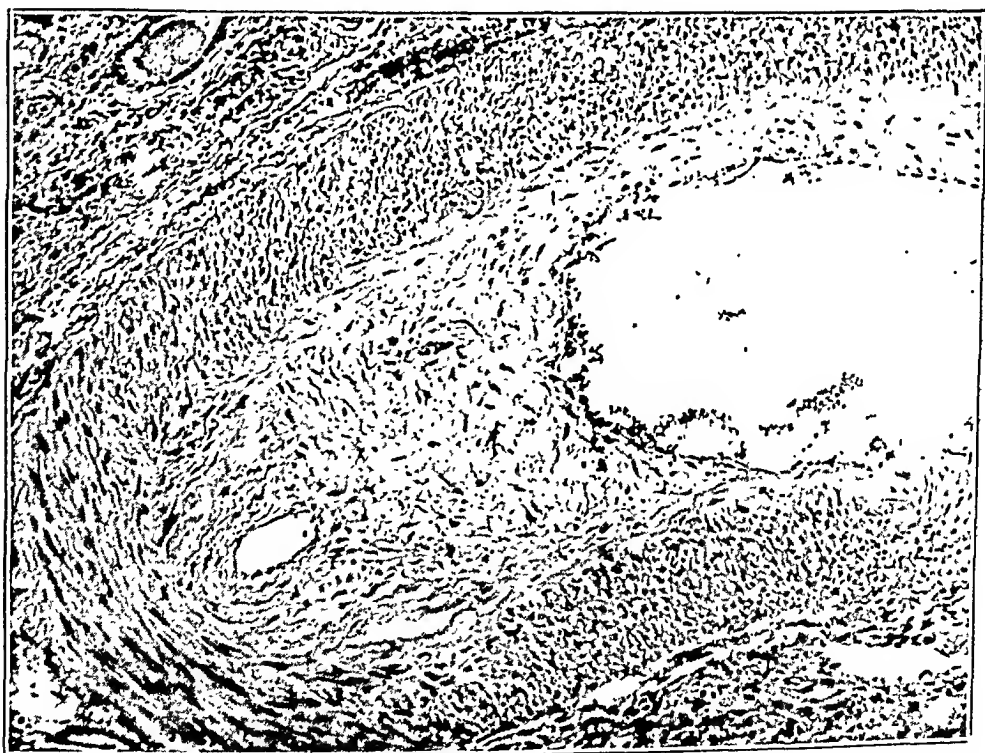


Fig. 3.—Photomicrograph ( $\times 106$ ) of a larger artery than those in figures 1 and 2, showing cellularity of the intima associated with conspicuous delicate fibrillar transformation.



The term transitional is purely arbitrary and has been chosen to designate those instances which we believe represent the anatomic transformation from the slowly progressive to the most advanced malignant (accelerated) phase of the disease. These cases were also designated thus to stress the interesting and important fact that a clinical picture of malignant disease may be observed in subjects who merely present conspicuous cellular intimal proliferations and no arteriolonecrotic lesions. Moreover, such a grouping serves to indicate that the intimal cellularity, edema and associated encroachment on the lumen are the precursors of the necrotic arteriolar alterations.

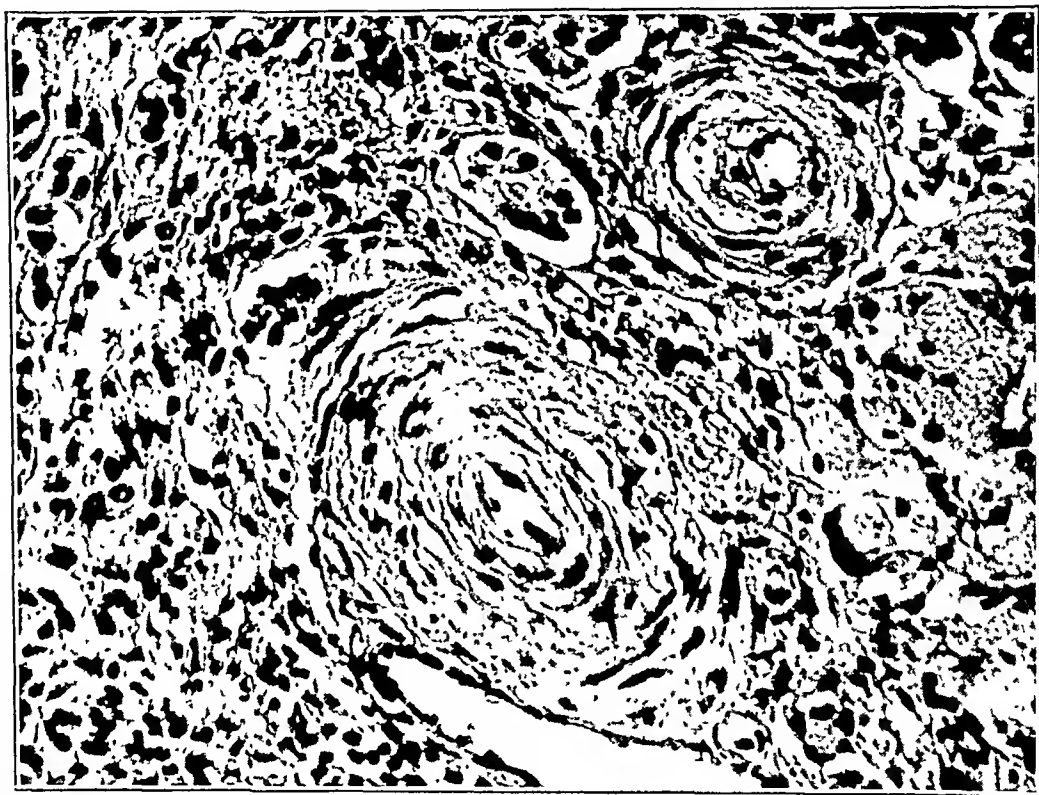


Fig. 4.—Photomicrograph ( $\times 335$ ) of interlobular arteries exhibiting an "onion peel" type of cellular proliferation of the intima with severe encroachment of the lumen. Note the looseness of the intima in the smaller artery.

**Advanced Form:** Arterial sections disclosed changes which were described both for the negative and for the transitional group. In the cases in the advanced group, however, even more prominent cellular proliferation was exhibited than was encountered in cases of the transitional phase, with more severe encroachment on the lumen. Frequently the cellular proliferations of the medium-sized and larger arteries were "nodular" in type, often concentric with uniform thickening of the wall of the vessel (fig. 4). Occasionally, due to the intimal edema and cellularity, the lumen was virtually occluded, while here and there com-



plete obliteration of the lumen had taken place. The cellularity of the intima was not confined to the interlobular arteries but was observed to have involved the walls of the arterioles and often of the arcuate

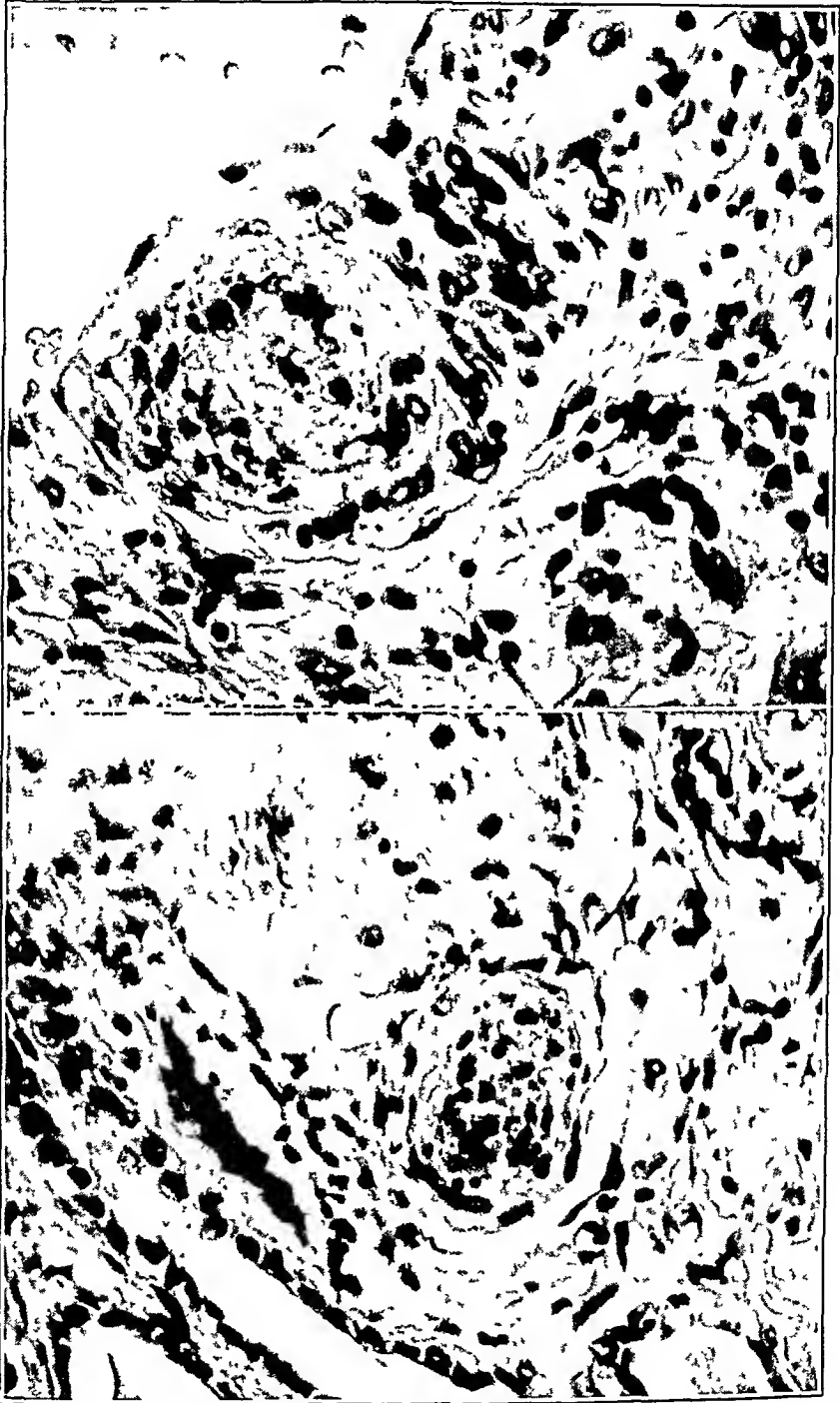


Fig 5—Photomicrograph ( $\times 400$ ) of arterioles presenting extensive necrosis and impregnation of the wall with erythrocytes.

vessels. A necrotizing arteritis similar to the type seen in the more acute form of the disease was observed in 1 case.

We were not impressed with any perivascular cellular collections which might be ascribed to the intimal alterations. If a perivascular infiltration was present, it was usually in those cases in which the inflammatory changes throughout the kidney were prominent. Consequently, such interstitial cellular reactions were ascribed to the basic generalized inflammatory renal involvement rather than to the presence of vascular abnormalities.

The arterioles and frequently the distal portions of the interlobular arteries were the seat of "fibrinoid" intimal transformations, diffusion of blood elements, mural necrosis, cellular degeneration and partial to

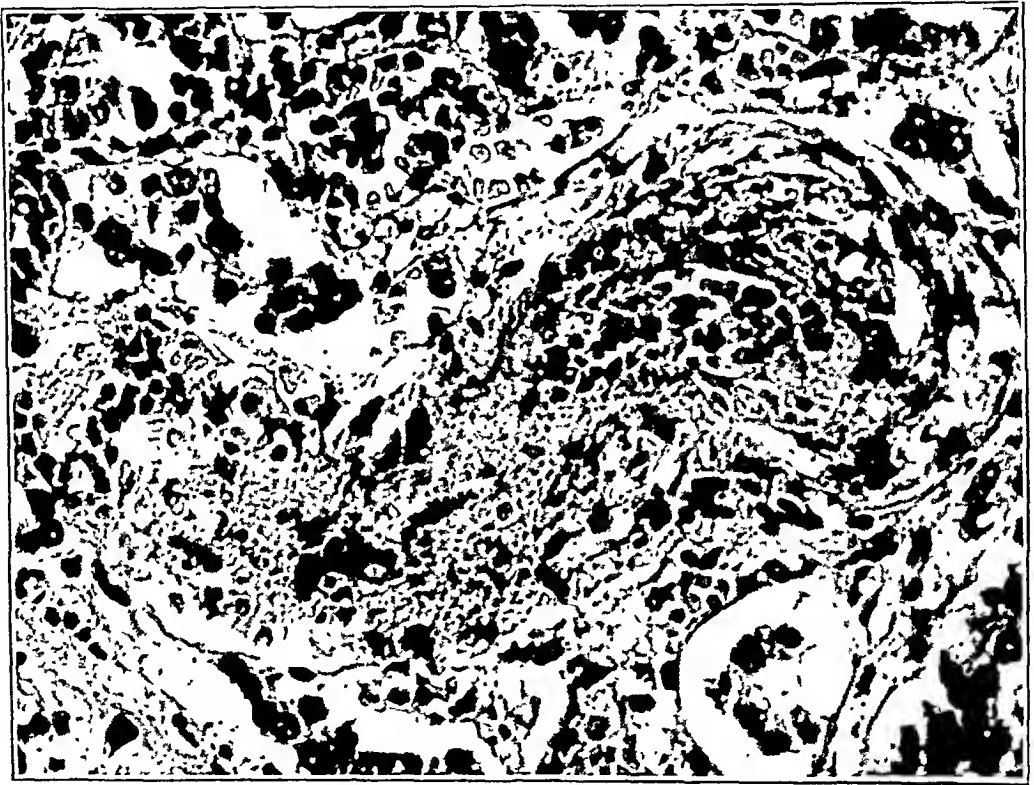


Fig. 6.—Photomicrograph ( $\times 480$ ) of a small interlobular artery showing widespread necrosis of the wall and associated diffusion of erythrocytes.

complete occlusive thromboses of their lumens (figs. 5 and 6). Arteriolar necrosis and rarely focal intimal necrosis of the smaller interlobular arteries were encountered in all cases which comprise this group. A periarteriolar polymorphonuclear reaction was seen only rarely. Occasionally, where the preglomerular portion of the vas afferens had become necrotic, extension of this process into the intraglomerular portion was observed. Here and there focal endothelial proliferation of various-sized arteries was also present. Rarely, fibrotic thickening of the walls of large veins was encountered, and in 2 instances, organizing venous thrombosis. In 1 case a so-called periarterial "granuloma" was

found consisting of newly formed capillaries, edematous connective tissue and infiltrating lymphocytes and polymorphonuclear leukocytes.

The lesions of the remaining structural units of the kidneys are too well known to be discussed here. It is worthy of mention, however, that in the accelerated group scattered areas of glomerular tuft necrosis were seen which were indistinguishable from those glomerular alterations that occur in the malignant phase of essential hypertension. Frequent intraluminal tubular collections of polymorphonuclear leukocytes were observed. In an occasional case low grade pyelonephritis was in evidence microscopically but was not considered to have contributed significantly to the renal alterations. The presence of polymorphonuclear leukocytes within the tubular lumen may be attributed not only to glomerular inflammation and coexistent pyelonephritis but to the internal hydronephrosis secondary to renal fibrosis. The analysis of our cases on the basis of the pathologic findings suggested the classification employed in table 4.

TABLE 4.—*Incidence of the Various Types of Arterial Change in Forty-Nine Cases of Chronic Diffuse Glomerulonephritis*

Type of Arterial Change	Number of Cases	Percentage of Cases
Slowly progressive arteriosclerosis.....	14	28.5
Accelerated arteriosclerosis		
Transitional phase.....	13	26.5
Advanced phase.....	22	45.0

#### DISTRIBUTION OF THE ARTERIAL LESIONS

Although the arterial lesions occurred more often and were most conspicuous within the kidney, they were not confined to that organ but presented a generalized distribution similar to that described by Fishberg.<sup>21</sup> The extrarenal vascular alterations in all groups consisted mainly of slight to moderate intimal thickening, elastosis and scattered foci of hyalinization.

Arterial lesions characteristic of accelerated arteriosclerosis in organs other than the kidneys were encountered less frequently. Scattered medium-sized arteries of the pancreas not uncommonly showed asymmetric intimal proliferations, foam cells and edema. Arteriolonecrosis was found in only 6 cases in extrarenal locations. In 2 instances arteriolar necrosis and a reactive polymorphonuclear infiltrate were encountered within the pancreas, while in 2 cases focal pancreatitis and

21. Fishberg, A. M.: *Anatomic Findings in Essential Hypertension*, Arch. Int. Med. 35:650 (May) 1925; footnote 3.

interstitial hemorrhages were observed, presumably the result of the vascular alterations. In 1 case thrombosis of the lumen of a medium-sized artery had occurred due to intimal and endothelial abnormalities. In 2 other subjects accelerated arterial lesions were present in the testes, stomach and adrenals.

#### CLINICOPATHOLOGIC SIGNIFICANCE OF ARTERIOPATHIES

Jores<sup>22</sup> was the first to stress the occurrence of generalized arteriosclerosis in subjects with glomerulonephritis and maintained that these vascular alterations might play a role in the clinical course of the disease. Baehr and Ritter<sup>23</sup> later demonstrated by means of perfusion experiments that a reduction in renal vasculature was characteristic of contracted kidneys and reported extensive renal arterial lesions in cases of chronic glomerulonephritis. That the vascular changes constituted an important factor in renal contraction in cases of glomerulonephritis was reiterated. The opinion was also posed that "this may help to explain why the clinical pictures in the advanced stages of both primary contracted and secondarily contracted kidney cannot be differentiated." Elwyn<sup>24</sup> and Weiss and Parker<sup>25</sup> similarly suggested that the arterial lesions which occurred in glomerulonephritis exaggerated the glomerular ischemia. These opinions were concurred in by Wagener and Keith,<sup>5</sup> who stated that when the sclerotic lesions occur in glomerulonephritis "they indicate that the nephritis had been complicated by the development of diffuse arteriolar lesions which from then on assume the dominant role in the progress of the disease." Fishberg<sup>15</sup> voiced a similar opinion.

The frequency with which severe vascular lesions may occur in instances of chronic diffuse glomerulonephritis is indicated by the observations which constitute the basis of this paper. In a group of 49 cases, advanced arterial changes were exhibited in 35, or 72 per cent (table 4). Correspondingly, the clinical course of illness in those cases in which the accelerated vascular lesions were encountered at necropsy was strikingly more severe than that in the cases in which this arteriopathy was absent. The constancy of the association of accelerated vascular lesions with a rapidly developing clinical course indicates that the anatomic lesions constitute an important mechanism in the intensification and progression of the clinical picture.

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22. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch. f. path. Anat.* **178**:367, 1904.

23. Baehr, G., and Ritter, S.: The Arterial Supply of the Kidney in Nephritis, *Arch. Path.* **7**:458 (March) 1929.

24. Elwyn, H.: Diffuse Glomerulonephritis, *Am. J. M. Sc.* **165**:366, 1923.

25. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18**:221, 1939.

## ETIOLOGY OF VASCULAR LESIONS

The vascular picture which we have encountered in our cases of chronic diffuse glomerulonephritis has been noted by a number of investigators and has been variously referred to either as productive endarteritis or as "endarteritis obliterans." These alterations have been attributed by some either to the presence of inflammatory changes or to the result of glomerular obstruction to blood flow<sup>15</sup> or to both.<sup>23</sup>

That obstruction to arterial blood flow of itself is an essential factor in the production of the accelerated type of lesion is negated by the fact that this picture is not observed in a disease, such as renal amyloidosis, in which glomerular obstruction is characteristically present,<sup>26</sup> unless, as we have seen, hypertension supervenes.

Weiss and Parker,<sup>25</sup> on the other hand, have implied an inflammatory origin for this variety of arteriopathy. In their cases, significantly, when hypertension was present, the vascular changes were found to be even more advanced and diffuse. That renal vascular changes may be of inflammatory origin and may even occur in the acute and the subacute phase of diffuse glomerulonephritis has been well recognized since Löhlein's<sup>27</sup> vivid description. The alterations which he described, however, were in the nature of arteriolitis or occasionally arteritis, with extensive necrosis of the wall, reactive polymorphonuclear leukocyte infiltrations and thrombosis of the lumen of the affected vessel. Vascular changes of this type were encountered in some of the cases of acute and of subacute glomerulonephritis which we reviewed as control material. It was apparent to us, however, that the type of lesion which Löhlein described in no way resembled the changes to which we specifically refer in this presentation. Moreover, the remarkable similarity of the arterial pictures of this phase of renal disease to those of unequivocal non-inflammatory renal diseases, such as the kidney of essential hypertension, vitiates the contention that inflammation plays an important role in their morphogenesis. It may be argued further in this connection that if the inflammatory changes of the renal parenchyma were significantly concerned in the formation of the cellular arterial proliferations and the arteriolar necrosis, one would expect this type of lesion to occur not only in the earlier stages of glomerulonephritis but more widely and more frequently. Indeed, instances of chronic diffuse glomerulonephritis

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26. Janeway, T. C.: Nephritic Hypertension: Clinical and Experimental Studies, *Am. J. M. Sc.* **145**:625, 1913.

27. Löhlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung für die Nephritis, *Arb. a. d. path. Inst. zu Leipzig* **4**:1, 1907.

in which the vascular alterations have been either minimal or wholly insignificant in character have been repeatedly observed by others<sup>28</sup> and by ourselves.

It may be stated, then, that the inflammatory process does not sufficiently account for the vascular lesions of accelerated arteriosclerosis described here, and the explanation, consequently, must be sought elsewhere. The possibility has also been suggested that hypothetic toxic material which originates in the presence of renal insufficiency is an etiologic force in the production of these lesions. That the vascular alterations, however, are not the result of such a mechanism is suggested by their absence in the slowly progressive group, since in all cases in this group the subjects had manifested varying degrees of azotemia. Furthermore, we have observed instances of malignant hypertension with renal arterial lesions of the identical form described in our cases of nephritic disease in which death was the result either of cerebral or of cardiac episodes and in which there was no evidence of renal insufficiency. The occurrence of arteriolonecrosis in the absence of renal insufficiency has been previously recorded.<sup>29</sup> We are not in accord, therefore, with the contention of some investigators<sup>30</sup> that the necrotic arteriolar lesions are the effect of functional renal impairment.

In our attempt to learn what common denominator exists in the cases with accelerated arteriopathy, to which might be possibly ascribed an etiologic role, we were struck with the constant association of severe protracted hypertension. This impression found substantiation when the clinical histories and the anatomic data were reviewed in cases of malignant nephrosclerosis. Except for the fact that the vascular lesions encountered in our cases of chronic diffuse glomerulonephritis were less widespread and intense, they did not differ basically from those seen in cases of malignant nephrosclerosis. Similarly, a history of sudden augmentation of a previously high blood pressure could be elicited not infrequently, just as in our cases of nephritic disease.

In the cases with mild to moderate increased blood pressure, retinal hemorrhages and exudates and arterial narrowing, but no swelling of the optic disk, the course is relatively benign, slow and progressive. Eventually, uremia makes its appearance, occasionally in conjunction with some component of cardiac insufficiency. The dominant arterial lesion here is the same as that which is seen in instances of so-called benign essential hypertension. In direct contrast to this picture are those cases in which the blood pressure is extremely high (systolic

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28. Fahr, T., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, vol. 6. Jores.<sup>22</sup>

29. Murphy, F. O., and Grill, J.: So-Called Malignant Hypertension: A Clinical and Morphologic Study, *Arch. Int. Med.* **46**:75 (July) 1930. Klemperer and Otani.<sup>2</sup>

30. Kimmelstiel and Wilson.<sup>4</sup> Weiss and Parker.<sup>25</sup>

over 200 mm. of mercury and diastolic exceeding 120 mm.). In addition to the retinal hemorrhages, exudates and arterial narrowing, there is swelling of the optic nerve head. The latter may vary from mere blurring of the disk margins to prominent elevation of the nerve head. The circumpapillary retinal tissue is sometimes edematous, and in cases of advanced disease detachment of the retina has been encountered. The clinical course of the latter group becomes intensified with the onset of severe hypertension and characteristically terminates due to an association both of renal and of cardiac failure—a picture which is identical with that observed in malignant nephrosclerosis. The visceral lesions also are strikingly similar to those encountered in the latter disease.

The third group—the transitional—occupies an intermediate place between the slowly progressive and the advanced accelerated one. It comprises instances of chronic diffuse glomerulonephritis in which the blood pressure is usually higher than that in the slowly progressive group and may reach the heights of the advanced accelerated group. In it, however, the blood pressure is usually more labile and neuroretinopathy may not be present. The histologic picture similarly lies midway between those just described. We are of the belief that the height and lability of the blood pressure and the presence or absence of neuroretinopathy are the cardinal clinical criteria on which to base the suspicion of the presence of either the slowly progressive or the accelerated phase of the disease. No other clinical manifestation (degree of azotemia, anemia or edema) can be employed in this connection.

Worthy of special mention are those cases of transitional disease in which excessive blood pressure had been present but in which anatomic lesions were encountered which were only slightly more advanced than those which were characteristic of the slowly progressive phase. It appears to us that these cases of transitional disease had reached their termination before there had been sufficient time for the development of the classic accelerated arteriopathy, which seems to indicate that severe hypertension may precede the development of the cellular and the necrotic arteriolar changes. When severe and fixed hypertension supervenes, the ischemia incident to the elevated intravascular tension is a factor in the acceleration of the tempo of the degenerative changes of the renal parenchyma, with resultant profound and irreversible disturbances of renal function.

#### SUMMARY AND CONCLUSIONS

A series of 49 consecutive cases of chronic diffuse glomerulonephritis was investigated, with especial attention focused on the character of the arterial changes in all viscera. An independent and thorough evaluation of the clinical data in these same cases was also made.

In accordance with the varied vascular pictures a division of the disease into a slowly progressive and an accelerated phase is proposed, 14 cases representing the former and 35 cases the latter.

The histologic vascular lesions peculiar to each group of cases are described in detail. The intimal fibrosis, elastosis of arteries and arteriolar hyalinization which were characteristic vascular alterations in the slowly progressive group were also observed in the other groups. A transitional group, in addition, exhibited cellular proliferation, foam cells and edema of the arterial intima, while the advanced accelerated group revealed an even more conspicuous cellular intimal proliferation of the arterial tree and, in addition, distinct necrosis of the arteriolar walls.

A correlation of the clinicopathologic features was then determined. In the majority of cases it was found that the intensity of the clinical picture usually paralleled the anatomic vascular changes.

Neuroretinitis, common in the transitional and the advanced accelerated group, was never observed in cases of the slowly progressive phase of the disease.

On the basis of this survey it is concluded that arterial alterations both in the transitional and in the advanced accelerated groups of cases of chronic diffuse glomerulonephritis represent the anatomic equivalents of the clinical picture which has been designated malignant hypertension. This has been shown to occur more frequently than hitherto suspected in chronic diffuse glomerulonephritis.

In view of the constancy of severe hypertension in a miscellaneous group of diseases in which accelerated arterial changes are present, this factor is considered a potent etiologic force in their production. Whether hypertension is the basic determinant for the appearance of the vascular lesion or is itself mediated through the liberation of a toxic vasopressor substance is beyond the scope of this presentation.

The tempo of the clinical course in instances of chronic diffuse glomerulonephritis may be influenced not only by the exacerbation of the inflammatory process but by the height of the blood pressure.

The occurrence of severe hypertension and neuroretinopathy in disease entities of varied pathogenetic background vitiates the belief that these criteria may be of differential diagnostic import.

The vascular lesions once established contribute importantly to the advancement of the renal process and the intensification of the clinical picture.

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# PYELONEPHRITIS AND HYPERTENSION

A STUDY OF THEIR RELATION IN 11,898 NECROPSIES

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CHICAGO

The work of Goldblatt<sup>1</sup> has shown that hypertension can be experimentally produced in animals by decreasing or altering the blood supply to the kidneys. Soon after the announcement of his experiments there began to appear in the literature clinical counterparts of his work. Mullholland<sup>2</sup> reviewed the literature in this regard and classified the reported cases of hypertension resulting from interference with the blood flow through the kidneys in the following manner:

I. Intrinsic, infection within the kidney

A. Bilateral, resulting from

1. Benign obstruction of the prostate
2. Partial obstruction of the ureters
3. Accompanying condition in the bladder causing clinical pyelonephritis
  - (a) Stone
  - (b) Diverticulum
  - (c) Malignant growth
4. Bilateral infection

B. Unilateral, resulting from

1. Pyelonephritis
2. Calculi
3. Contracted kidney caused by
  - (a) Trauma
  - (b) Infection
4. Tuberculosis of kidney

II. Extrinsic, effecting interference with the circulation in the renal artery

Unilateral

1. Malposition
2. Abnormal course and position of artery
3. Atheromatous plaques
4. Infarct of the kidney
5. Thrombosis with recanalization
6. Hydronephrosis with pressure on artery

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1. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia: Harvey Lecture, Bull. New York Acad. Med. **14**:523, 1938.

2. Mullholland, S. W.: Hypertension: The Problem, the Study, the Future, Bull. New York Acad. Med. **16**:244, 1940.

Among the most numerous of these are the cases of unilateral pyelonephritis associated with hypertension apparently cured by nephrectomy (McIntyre,<sup>3</sup> Barker and Walters,<sup>4</sup> Barney and Suby,<sup>5</sup> Boyd and Lewis,<sup>6</sup> Butler<sup>7</sup> and Leadbetter and Burkland<sup>8</sup>).

Accepting pyelonephritis as one of the causes of disturbed renal vascular flow and thus a process capable of invoking hypertension, Weiss and Parker<sup>9</sup> have attempted to explain and correlate the frequent finding of vascular changes of the kidney in 100 cases of pyelonephritis and hypertension. Their results were constant and seemed to show a distinct relation to the degree of hypertension and the age of the infection. Though their study deals with the entire field of pyelonephritis, the most noteworthy part is that regarding hypertension. They observed elevation of blood pressure especially in the healed and the chronic stage of the infection and were able to describe the vascular lesions in great detail. Their dissociation of the intimal thickening and hyalinization as a result of involutionary changes from productive endarteritis, hyperplastic arteriosclerosis and necrotizing arteriolitis which they were able to identify only in cases of pyelonephritis, and these were most pronounced in the infected and scarred portions of the kidneys, seems to prove that the vascular lesions are the result of the infection and probably a factor in the production of hypertension. They found similar lesions, though of a lesser degree, in cases of infection without hypertension and concluded that the lesions occur before the hypertension develops. The subsequent hypertension apparently aggravates the lesions, which in turn aggravate the high blood pressure, thereby provoking a vicious cycle.

The purpose of this study is to examine critically the autopsy records of a large series of patients and to correlate the incidence of hypertension and pyelonephritis. Records of patients with hydro-

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3. McIntyre, D. W.: Unilateral Pyelonephritis with Hypertension: Apparent Cure After Nephrectomy, *J. Urol.* **41**:900, 1939.

4. Barker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treated by Nephrectomy, *Proc. Staff Meet., Mayo Clin.* **13**:118, 1938.

5. Barney, J. D., and Suby, I. H.: Unilateral Renal Disease with Hypertension: Report of a Case Apparently Cured by Nephrectomy, *New England J. Med.* **220**:744, 1939.

6. Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, *J. Urol.* **39**:627, 1938.

7. Butler, M.: Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16**:889, 1938.

8. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, *J. Urol.* **39**:611, 1938.

9. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18**:221, 1939.

nephrosis, nephrolithiasis and horseshoe kidney were also studied to complete the picture. The relation of renal vascular lesions to hypertension, especially as regards age and the state of vascular tension, as well as sex and race, were particularly noted. It is thought that such a study of a large series of patients may contribute to the collection of statistical information already begun by such observers as Weiss and Parker and the Mount Sinai group in New York,<sup>10</sup> as well as by the group at the Mayo Clinic<sup>11</sup> and others.

All instances of pyelonephritis were studied from records of 11,898 consecutive patients who came to autopsy at the Cook County Hospital in the ten year period 1930 to 1939 inclusive. These patients were tabulated according to age, sex, race and the state of vascular tension. The patients with unilateral and with bilateral involvement of the kidneys were separated. The complete autopsy protocol, which at the Cook County Hospital consists of an abstract of the clinical history and course of the disease, a description of the body as a whole, a gross description of each organ, an objective description of the microscopic appearance of the pertinent organs and a detailed anatomic diagnosis, was examined critically. For criteria of hypertension a persistent systolic pressure of 150 mm. of mercury and a diastolic pressure of 95 mm. were selected; these are well above the limits accepted by the American Heart Association.<sup>12</sup> A hypertrophied left ventricle and increased weight of the heart in the absence of other known causes was considered substantiating evidence. If the recorded blood pressure was a terminal one or was equivocal, the anatomic evidence was accepted.

There were 290 patients with pyelonephritis, constituting 2.5 per cent of the total number. Of these, the condition was bilateral in 224 and unilateral in 66. The patients with bilateral disease constituted 77 per cent of those with pyelonephritis and 1.7 per cent of all the patients in the series. There were 130 females and 160 males, 44.8 and 55.2 per cent, respectively. This is more or less in accord with the proportion of adult males and females on whom autopsy was done.

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10. Oppenheimer, B. S.; Klemperer, P., and Moschowitz, L.: Evidence for Goldblatt Mechanism for Hypertension in Human Pathology. *Tr. A. Am. Physicians* 54:69, 1939.

11. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney. *Proc. Staff Meet., Mayo Clin.* 15:477, 1940. Barker, N. W., and Walters, W.: Hypertension and Chronic Atrophic Pyelonephritis, *ibid.* 15:475, 1940. Braasch, W. F., and Jacobson, C. E.: Chronic Bilateral Pyelonephritis and Hypertension, *ibid.* 15:481, 1940.

12. New York Heart Association, Criteria Committee. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*, ed. 4, New York, New York Tuberculosis and Health Association, 1939.

Of the 290 patients, 200, or 68.9 per cent, were white and 90, or 31.1 per cent, were Negro.

The patients were arbitrarily divided into six age groups: 30 and under, 31 to 40, 41 to 50, 51 to 60 and over 60. Thirty-six patients were under 30, of which 13 were male and 23 female. Between the ages of 31 to 40 there were 45 patients, of which 14 were male and 31 female. In the group from 41 to 50 there were 56, more or less equally divided between the sexes. In the 51 to 60 group there were 65, of which 35 were male and 30 female. In the patients over 60 there were 69 men and 19 women. The preponderance of males in the total number of patients with pyelonephritis is made up mainly by those in the older age groups. The incidence of pyelonephritis in the young women not only fits in with expectations but explains to a great extent the mortality. One can almost assume from these figures that fewer women survive such renal infection and live to be autopsied in the

TABLE 1.—*Incidence of Hypertension in the Various Age Groups in Two Hundred and Ninety Patients with Pyelonephritis*

Age Group	Hypertension, %	Renal Vascular Damage, %
Under 30.....	28.0	29.0
31-40.....	33.3	33.3
41-50.....	41.0	49.0
51-60.....	49.0	56.0
Over 60.....	63.0	69.0
Average.....	44.4	50.6

aged group. Though it was impossible to separate in this study the patients with acute, chronic and healed pyelonephritis, it is likely that the young women died in the acute stage. The incidence of pregnancy in these women was not ascertained, but the great preponderance of the disease in the women of child-bearing age is of some significance.

Forty-four and four-tenths per cent of all of the patients regardless of age, sex and race had an elevation of blood pressure. However, the significant findings are those seen in the incidence of hypertension in the various age groups (table 1). From 28 per cent in the youngest group the incidence rises in direct proportion to age until it reaches 63 per cent in the oldest group. Similarly, the incidence of renal vascular changes, which in this series includes all the various types described by Weiss and Parker with few patients showing only one distinct type, is completely parallel with that of hypertension. It increases from 29 per cent in those under the age of 30 to 69 per cent in those over 60. The greatest incidence of pronounced hypertension was found in the atrophic kidneys of patients with old pyelonephritis with microscopic pictures of well advanced arteriolosclerosis.

Of the 66 patients with unilateral pyelonephritis, 22, or 33.3 per cent, had an elevated blood pressure (table 2). The greatest incidence of hypertension occurred in the 41 to 50 age group, being 35.7 per cent, as compared to 28.5 per cent in the youngest group. In the category of bilateral pyelonephritis 107 patients, or 47.7 per cent, had high blood pressure. The percentage ranged from 27.5 in the youngest group to 63.7 in the oldest one. It appears that any increased incidence of

TABLE 2.—*Relation of Hypertension to Unilateral or Bilateral Involvement of the Kidneys in Two Hundred and Ninety Patients with Pyelonephritis*

Age Group	Unilateral Involvement			Bilateral Involvement		
	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients
	No. of Patients	Percentage		No. of Patients	Percentage	
Under 30	2	28.5	5	8	27.5	21
31-40	3	33.3	6	12	33.3	24
41-50	5	35.7	9	18	42.8	24
51-60	6	35.3	11	26	54.2	22
Over 60	6	31.5	13	43	63.7	26
Total.....	22	33.3	44	107	47.7	117

TABLE 3.—*Relation of Hypertension to Sex in Two Hundred and Ninety Patients with Pyelonephritis*

Age Group	Male			Female		
	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients
	No. of Patients	Percentage		No. of Patients	Percentage	
Under 30	5	38.4	8	5	21.7	18
31-40	5	35.7	8	10	32.2	21
41-50	14	48.2	15	9	33.3	18
51-60	21	69.0	24	11	36.6	19
Over 60	42	62.1	27	7	36.8	12
Total.....	87	54.3	83	42	32.9	88

hypertension in patients with pyelonephritis occurs mainly in those in whom the kidneys are bilaterally involved, as compared to those in whom involvement is unilateral.

The relative preponderance of pyelonephritis in young women as compared to its incidence in young men has already been mentioned. Only 32.9 per cent of the women had hypertension, as compared to 54.3 per cent of the men. This relative infrequency of high blood pressure in females as compared to that in males persists through all the age groups except that of 31 to 40, in which the difference is not striking (table 3). Among the Negroes there appeared to be a greater

incidence of hypertension in patients 31 to 50 years of age as compared to that in white persons of the same age, though the total incidence is 46.5 per cent in the white patients and 40 per cent in the Negroes (table 4).

Seventeen patients in the series had horseshoe kidney, 13 males and 4 females. Of these, 11, or 64.7 per cent, had elevated blood pressure (table 5). In these, discounting the single patient under the

TABLE 4.—*Relation of Hypertension to Race in Two Hundred and Ninety Patients with Pyelonephritis*

Age Group	Negro			White		
	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients
	No. of Patients	Percentage		No. of Patients	Percentage	
Under 30	3	21.4	11	7	31.8	15
31-40	9	39.0	14	6	27.2	16
41-50	9	45.0	11	14	38.8	22
51-60	8	44.4	10	24	51.0	23
Over 60	7	46.6	8	42	57.5	31
Total.....	36	40.0	54	93	46.5	107

TABLE 5.—*Incidence of Hypertension in Seventeen Patients with Horseshoe Kidney, Thirteen Patients with Polycystic Kidney and Sixty-Two Patients with Nephrolithiasis*

Age Group	Horseshoe Kidney		Polycystic Kidney		Nephrolithiasis	
	Elevated Blood Pressure	Normal Blood Pressure	Elevated Blood Pressure	Normal Blood Pressure	Elevated Blood Pressure	Normal Blood Pressure
Under 30.....	1	0	1	0	2	2
31-40.....	1	1	2	0	4	7
41-50.....	4	1	1	4	6	6
51-60.....	2	2	2	2	8	10
Over 60.....	3	2	0	1	13	4
Total.....	11 (64.7%)	6	6 (46.15%)	7	33 (53.2%)	29

age of 30, the greatest incidence of high blood pressure occurred in patients between the ages of 41 to 50, of whom 4 of 5 had hypertension. Here again the finding of vascular sclerosis was directly proportional to the incidence of hypertension. Thirteen, or 0.11 per cent, of the 11,898 patients in the series had polycystic kidneys; 10 patients were male, and 3, female. Of these, 7, or 53.7 per cent, had an elevated blood pressure. The renal vascular damage in these patients was not outstanding, 6 of 13 showing no particular parenchymal changes except atrophy in cases of severe disease. It may be pointed out that the hypertension resulting from polycystic kidney is thought to occur

differently from that of pyelonephritis. It is said to be the result of pressure of the cysts extrinsically on the renal artery. The lack of renal vascular damage in these patients corresponds with Goldblatt's finding of the relative absence of such damage in the ischemic kidneys of his dogs. Sixty-two patients had nephrolithiasis, comprising 0.52 per cent of the total number of patients. It was unassociated with evident pyelonephritis, the patients in this study with both conditions being included among those with pyelonephritis. Of these, 43, or 53.2 per cent, had an elevated blood pressure.

Braasch in his control series of 975 patients admitted to the Mayo Clinic found 20 per cent had hypertension, as compared to 26 per cent of 180 patients with pyelonephritis. The incidence of hypertension both in the control series and in the patients with renal disease increased with the age of the patients. In the youngest group there was an incidence of 8.4 per cent in the controls, as compared to 13.3 per cent in those persons with pyelonephritis; while in the oldest patients the incidences were 47.1 and 53 per cent, respectively. Oppenheimer, Klemperer and Moschowitz<sup>10</sup> selected every fifteenth patient in their series of 5,000 who came to autopsy and found 24 per cent had high blood pressure, as compared to 40 per cent of 97 patients with pyelonephritis. For control of the study reported here approximately 1,000 of some 12,000 patients on whom autopsy was performed during the ten year period were selected at random and classified according to age group and sex, as well as the presence or absence of hypertension. The same standards were used in the tabulation of the control patients as were used for patients with pathologic conditions. Though no exact tally was kept, approximately every tenth to fifteenth patient in the entire group of 11,898 was selected. It is felt that the resultant group represents a good cross section of the autopsy material at the Cook County Hospital and serves as a good basis for comparison. In the entire group 331 patients of 947, or 34.9 per cent, had an elevation of blood pressure. If one segregates these patients into the age groups used in the study, the percentage incidence of hypertension is under 30, 15.6; 31 to 40, 28.1; 41 to 50, 40; 51 to 60, 36.6, and over 60, 43.1. In the males the incidence in the same groups is 21.4, 25.5, 39.8, 33.5 and 43.7. In the females it is 10, 30.6, 40.2, 43.07 and 42.1 (table 6).

On the surface it would appear that 44.4 per cent of patients with pyelonephritis, 53.2 per cent of those with nephrolithiasis, 64.7 per cent of those with horseshoe kidney and 53.8 per cent of those with polycystic kidney showed an elevation of blood pressure, as compared to 34.9 per cent of a control group. The number of patients with polycystic kidney is too few for analysis. In the patients with pyelonephritis there appears to be a distinct increase in the incidence of hypertension

as compared to that in the controls except in the age group 31 to 50, in which the incidence is almost parallel. Comparing the female patients with pyelonephritis with the female controls the incidence seems to be greater only in the youngest group, in which it is 21.7 per cent, as compared to 10.0 per cent. Indeed, in the women over 40 the incidence of high blood pressure is greater in the control group. However, in the men the incidence of hypertension is greater in comparison in all the age groups and is most marked in men over 40. This apparently occurs in patients in whom both kidneys are involved, those with unilateral involvement showing no distinct variation. Though only 64 patients had uncomplicated nephrolithiasis, the incidence of hypertension was more striking than in those with the

TABLE 6.—*Relation of Hypertension to Sex and Age in One Thousand Control Patients*

Age Group	Male			Female		
	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients	Elevated Blood Pressure		Normal Blood Pressure: No. of Patients
	No. of Patients	Percentage		No. of Patients	Percentage	
Under 30	12	21.4	44	6	10.0	53
31-40	24	25.5	70	23	30.6	52
41-50	57	39.8	86	31	40.2	46
51-60	46	33.5	91	28	43.1	37
Over 60	69	43.7	89	35	42.1	48
Total.....	208	35.3	380	123	34.9	236

other diseases, being 53.2 per cent of all the patients, compared to 34.9 per cent of the controls.

The increasing incidence of hypertension with age in all the patients is of some significance. Two possible explanations may be offered. The frequency with which high blood pressure occurs in elderly persons without renal damage may suggest that even without pyelonephritis hypertension would have been present (this seems to be borne out by the controls), and therefore pyelonephritis is not an important factor in the production of their hypertension. The other explanation is that the occurrence of a much greater incidence of hypertension in the older age groups is in complete accord with the concept that the time element is important in the evolution of the hypertension associated with pyelonephritis. This material does not show how long the patients had had their renal infection, but one may assume that a patient over 60 has had it longer than a patient under 30. If one remembers that these studies are based on autopsy records, and that the young patients either did not survive their renal infection or succumbed to an unrelated



disease process, it is easily understood that the time element as regards the age of the infection may be of some importance in the production of hypertension. The apparent paradox of the women over 40 in the control group having a greater incidence of hypertension than the similar group with pyelonephritis can be rationalized. The control patients being a cross section of all those who came to autopsy include ones with all types of hypertension; some of them may be duplications as the result of pyelonephritis. In women over 40 degenerative diseases, some of which are accompanied by hypertension, are apt to occur. In addition, the great incidence of pyelonephritis in young women seems to indicate that fewer women survive their infection and live long enough to be autopsied in an older age group. If this is true, then the women over 40 in the control group are patients who not only survived their renal infection long enough for hypertension to develop but lived long enough to have an elevated blood pressure from other causes.

#### SUMMARY

The incidence of hypertension in patients with pyelonephritis was studied from 11,898 autopsies performed in a ten year period. In these the incidence was 44.4 per cent as compared to 34.9 per cent in a control group selected at random. In an analysis, however, this greater incidence apparently occurred in patients with bilateral pyelonephritis, especially in the male sex, and was most marked in men over 40. The relative absence of high blood pressure in patients with unilateral pyelonephritis was striking. The incidence of hypertension increased with the age of the patient and was parallel to the incidence of marked renal vascular damage. In small groups of patients with polycystic kidney, horseshoe kidney and uncomplicated nephrolithiasis the incidence of hypertension was 46.15, 64.7 and 53.25 per cent respectively.

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# INTERMITTENT FEVER OF UNKNOWN ORIGIN

RECURRENT HIGH FEVER WITH BENIGN OUTCOME IN A PATIENT  
WITH MIGRAINE AND NOTES ON "NEUROGENIC" FEVER

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"Neurogenic" fever is a term the limits of which have not been clearly defined. Lesions of the brain stem or the hypothalamus are known to be associated frequently with pyrexia.<sup>1</sup> Typhoid vaccine and other foreign protein agents cause fever probably by functional alterations in the central nervous system.<sup>2</sup> Whether this effect occurs by virtue of changes in circulation or by direct chemical action on cells of the thermoregulatory apparatus is not yet clear. Even less clear is the mechanism responsible for elevations of body temperature accompanying emotional disturbances. The fact that they do occur, however, has long been known. Most of the writing on the subject has appeared in the German literature. Friedmann and Kohnstamm<sup>3</sup> in 1914 recognized that fever frequently accompanied excitement and emotional tension in the absence of physical overactivity. Seven years later Eichelberg<sup>4</sup> was able to induce temperatures up to 39.2 C. (102.5 F.) in patients by hypnosis. Since then pyrexia has been observed in a variety of emotional settings. Osler<sup>5</sup> recognized it as a manifestation of "hys-

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Dr. Herbert S. Ripley saw the patient frequently in consultation and supplied some of the data regarding his personality.

1. Kleynyens, F.: *Recherches sur la physiopathologie des centres thermorégulateurs*, *Compt. rend. Soc. de biol.* **132**:55, 1939.

2. Ranson, S. W.; Clark, G., and Magoun, H. W.: *Effect of Hypothalamic Lesions on Fever Induced by Injection of Typhoid-Paratyphoid Vaccine*, *J. Lab. & Clin. Med.* **25**:160, 1939.

3. Friedmann, M., and Kohnstamm, O.: *Zur Pathogenese und Psychotherapie bei Basedowscher Krankheit*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **23**:357, 1914.

4. Eichelberg: *Durch Hypnose erzeugtes "hysterisches Fieber"*, *Deutsche Ztschr. f. Nervenhe.* **68**:352, 1921.

5. Osler, W.: *The Principles and Practice of Medicine*, ed. 3, New York, D. Appleton and Company, 1898.

teria." Reimann<sup>6</sup> found low grade temperature elevations in a group of psychoneurotic patients who showed tachycardia, wide pupils, dry mouth and hypoperistalsis. Dejerine<sup>7</sup> wrote that temperature elevations might be readily attributed to emotional causes in the absence of demonstrable physical disease. Unfortunately, reports of actual instances of such fevers are vague, and the personality reaction types in which the fevers occur are not clearly defined. On the basis of the knowledge which has accumulated already, however, it is possible to classify instances of "neurogenic" fever under four headings.

First, there is the occurrence of extremely high temperatures generally held to be incompatible with life in a person who does not otherwise appear ill. It is likely that in most cases fraud is the basis of such a fever. The second variety is habitual low grade fever.<sup>8</sup> The third type is manifested by isolated rises in body temperature of short duration definitely associated with some experience inducing anxiety or tension in the patient.<sup>9</sup> The last group includes recurrent bouts of high fever, which continue for years without apparent detriment to the patient. This communication will deal with a case of the last-named type of fever.

A competent short review of the literature on this subject between 1910 and 1933, with abstracts of illustrative cases, is available.<sup>10</sup> There are few reports in detail of cases of recurrent fever over a period of years which eluded explanation indefinitely on the basis of some structural disease.

Alt and Barker in 1930<sup>11</sup> reported a case of intermittent fever which occurred in a 17 year old Armenian boy and which had lasted twenty-five years at the time the report was made. Attacks occurred about four times a year at first and gradually increased in frequency, until at the time the case was reported the patient was having an attack twice a week. The temperature rose to 39 C. (102.2 F.). Abdominal cramps on the right side, vomiting, pain in the knees and leukocytosis (15,000 to

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6. Reimann, H. A.: Hypothermia: Subnormal Temperature and Its Relation to Neurocirculatory Asthenia, *J. A. M. A.* **115**:1606 (Nov. 9) 1940.

7. Dejerine, J.: *Sémiologie des affections du système nerveux*, Paris, Masson & Cie, 1926, p. 1070.

8. Smith, D. S.: Fever of Undetermined Etiology, *J. Michigan M. Soc.* **38**: 125, 1939.

9. Falcon-Lesses, M., and Proger, S. H.: Psychogenic Fever, *New England J. Med.* **203**:1034, 1930.

10. Dunbar, H. F.: *Emotions and Bodily Changes*, ed. 2, New York, Columbia University Press, 1939.

11. Alt, H. C., and Barker, M. H.: Fever of Unknown Origin, *J. A. M. A.* **94**:1457 (May 10) 1930.

20,000 cells) were often associated with the fever. The episode lasted about a day and was usually followed by loose stools for a day or two. Otherwise, between the attacks the patient felt perfectly well. He did not lose any weight or show any signs of infection except for an enlarged spleen. The latter was removed surgically, without effect on the bouts of fever. It weighed 544 Gm. at operation. Microscopic section revealed nothing specific or helpful diagnostically.

The next year Santos<sup>12</sup> reported 2 cases of a similar condition. In 1 case a 32 year old woman had recurrent febrile rises of temperature to 41 C. (105.8 F.) associated with abdominal cramps. During a period when attacks were occurring nearly every day the author found it possible to suspend them for several days with the help of hypnotic suggestion. In the second case a 24 year old woman was subject to hysterical palsies and aphonia and convulsive attacks; she also had abdominal pain in association with her fever. The fever could be controlled by injection of opiates.

Later Scott and Kirschner<sup>13</sup> reported a case in which attacks of *féver* were accompanied by an urticarial cutaneous rash, joint pains and at one time an effusion into the right knee joint.

In 1937 Allen<sup>14</sup> reported a case of intermittent hyperthermia of seven years' duration, which now, five years later, is the subject of the present communication.

#### REPORT OF A CASE

The patient, L. McC., an engineer aged 43 at the time of admission to the New York Hospital, began suffering from intermittent attacks of fever with temperatures up to 40 C. (104 F.) in 1928, and he has continued to be afflicted with them until only recently.

It is of special interest that the patient's father had suffered from similar intermittent attacks of fever with temperatures up to 40 C. associated with "sick headache," nausea and vomiting. These began at about the age of 25, lasted nearly fifteen years and finally stopped spontaneously. At first the bouts came every few weeks, but toward the end they were less frequent, occurring only two or three times a year. A sister and an aunt of the patient suffered most of their lives with periodic headaches without fever, diagnosed by physicians as migraine. At the time of the menopause the patient's mother had a mental illness which required treatment in a sanatorium for several months.

During late adolescence the patient himself began suffering from periodic headaches characterized by bifrontal pain and pain in the eyeballs, photophobia and nasal discharge. The occurrence was especially frequent at times of emotional

12. Santos, R. N.: Ueber die neuropsychogene Hyperthermie, *Med. Klin.* **27**: 1273, 1931.

13. Scott, J. W., and Kirschner, A.: Intermittent Fever of Three and a Half Years' Duration, *Lancet* **2**:299, 1938.

14. Allen, E. V.: Intermittent Hyperthermia of Seven Years' Duration, *Ann. Int. Med.* **10**:1204, 1937.

strain. In 1922, at 25 years of age, during a period of marked anxiety in a setting of business problems he became nearly incapacitated by these headaches. Twelve years before admission to the New York Hospital, at the age of 31, the patient suddenly ceased to have the headaches and he began to experience recurrent attacks of a different nature, characterized by fever, malaise and aches and pains in his back and extremities. One or two days after his first episode he felt well again. Six weeks later a second attack occurred. From then on he had recurrent bouts of fever with progressively shorter intervals between them, until at the time of admission to the New York Hospital he was having one a week. Before each episode for a day or less there were prodromal symptoms consisting of aches in the ankles and the spine, a feeling of mental unrest and difficulty in concentration. The fever was often ushered in by a shaking chill. The temperature rose rapidly to a peak and returned to normal within twelve hours. Leukocytosis (in the neighborhood of 15,000 cells) occurred. The episodes associated with marked elevation of temperature, to about 40 C., were of shorter duration and caused less discomfort than those in which the fever was of relatively low grade or was artificially depressed by antipyretic drugs. After the fevers he had a "purged" feeling, with a sense of especial well-being and mental efficiency. From this point on, he could do his work effectively until the prodromal symptoms of the next attack appeared.

As already mentioned, these fevers could be modified by antipyretic drugs, such as acetylsalicylic acid and aminopyrine, but the attacks could not be thus prevented.

One measure which altered the time of occurrence of attacks was the induction of fever by the administration intravenously of killed typhoid organisms. The sharp febrile episode resulting from this was apparently identical with the attacks which occurred spontaneously. When such an artificial fever was induced on the eighth day after an attack, the next fever occurred ten days after the artificial one. This phenomenon has been repeatedly utilized by the patient to avert attacks which would normally fall on days on which he had some important job to do.

Statistical data on the distribution of attacks show that they had their onset most frequently at night, especially the severer ones. They occurred least often in the late afternoon. The interval between attacks lengthened when the patient was satisfactorily occupied and shortened when he was inactive, especially if under observation or hospitalized. Over all, the intervals between attacks became progressively shorter.

The fevers were not associated with loss of weight or debility, nor was there any evidence between attacks that the patient was ill. After five years of fevers appearing with increasing frequency he had his first remission. It was apparently spontaneous, and it lasted one hundred days. During this time his headaches, which had been suspended while he was having recurrent febrile attacks, recurred. Two years later he was admitted to the Mayo Clinic, where he was studied intensively. The only clue to the origin of the fevers was the finding of the same strain of alpha Streptococcus in his nasopharynx, tonsils and prostatic secretion. He was given a course of therapy with Rosenow's hyperimmune serum, from which he acquired serum sickness. After this his tonsils were removed, and subsequently his second remission occurred. This one lasted four and one-half months. The details of the history up to this time and the results of the studies at the Mayo Clinic are contained in Allen's paper.<sup>14</sup>

During the remission the patient began to suffer again from periodic headaches. With the recurrence of the fevers, however, the headaches once again stopped.

On March 8, 1940, the patient entered the Stanford University Hospital for study. The following data are supplied by Dr. Arthur L. Bloomfield. General

physical examination and examination of sensory and motor functions revealed nothing abnormal. Routine blood counts were normal except for the temporary leukocytosis which accompanied the bouts of fever. Blood cultures and agglutination reactions were negative for paratyphoid bacilli of types A and B, *Salmonella suipestifer*, *Brucella abortus*, *Brucella melitensis* and *Brucella suis*, as well as *Bacillus tularensis*. The agglutination test for typhoid organisms gave a positive reaction (*vide* numerous intravenous injections of killed typhoid organisms). The cutaneous reaction to coccidioidin was negative. Examinations of urine and feces, including repeated cultures, showed nothing abnormal. Culture of the prostatic secretion revealed 600 colonies of beta hemolytic *Streptococcus* per cubic centimeter. The Wassermann reactions of the blood and the spinal fluid were negative; the remainder of the examination of the spinal fluid revealed nothing abnormal. An electrocardiogram and an electroencephalogram were normal, as were roentgenograms of the skull and the chest and excretory pyelograms. The basal metabolic rate ranged between  $-1$  and  $+15$  per cent. Psychometric examination showed an intelligence quotient of 149. The erythrocyte sedimentation rate was repeatedly within normal limits.

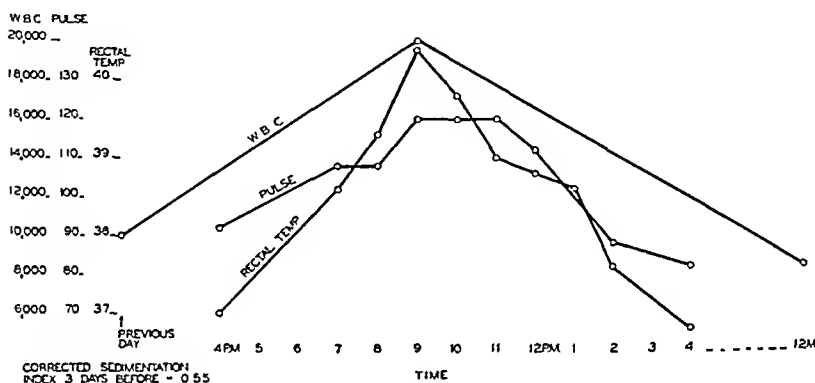
In the Stanford University Hospital, after the possibility of malingering had been carefully excluded, various therapeutic measures were undertaken without avail in an effort to eliminate the fevers, including administration of sulfanilamide, roentgen therapy over the cervical region and attempts at hypnosis. The latter failed because the patient resisted the procedure, unwilling to lose "an infinitesimal part of my will." One interesting finding came out of these studies, however. It was observed that vasomotor changes were associated with changes in the emotional state of the patient to the extent that it was possible to raise the cutaneous temperature of one extremity merely by suggestion. He was even able to accomplish this feat by autosuggestion. In such an attempt at autosuggestion later in the New York Hospital it was found that the cutaneous temperature of his right leg was raised 0.5 C. (0.9 F.) above that of his left leg as measured under basal conditions with a radiometer. The patient was discharged from Stanford University Hospital May 1. It was thought that the fevers resulted from an obscure infection, although the possibility of a neurogenic basis was entertained.

The patient was referred to the New York Hospital for further studies, with special attention to the mechanism of heat production. He was admitted on May 31, 1940 and studied in attacks much as he had been elsewhere. Since the likelihood of bacterial origin in the fevers had been pretty well excluded, more emphasis was placed on the possibility of virus origin. Accordingly, spinal fluid, blood and duodenal contents were collected during the height of fever and injected into mice and guinea pigs by Dr. Thomas P. Magill. Efforts thus to isolate a virus were unsuccessful. In view of the fact that the patient did not appear sick or debilitated in any way after twelve years of such vigorous illness it was held unlikely that his disease was infectious in nature. The figure illustrates the course of the rectal temperature and the pulse during a typical attack. The degree of leukocytosis is also recorded. Oral and axillary temperatures were also taken. The values were slightly lower than those of the rectal readings, as is usually found.

The relation of the bouts of fever to his "migraine" headaches was striking, particularly the fact that when the fevers started, the headaches to which he had been subject periodically ended, only to recur during the two periods of remission from the fevers. It seemed as if the two conditions were separately existing components of the same derangement. This relation suggested that the fevers might be due to a circulatory disturbance in the thermoregulatory centers. It is known that the headache of migraine is caused by excessive dilatation of chiefly extra-

cranial arteries of the head.<sup>15</sup> It is also known that in certain cases of migraine there occurs vasoconstriction of intracranial arteries, usually in the preheadache stage.<sup>16</sup> It was postulated that some such vasomotor derangement in the hypothalamus might be responsible for the febrile rises.

To test this possibility an attempt was made to abort febrile attacks by the administration of vasodilators, namely, glyceryl trinitrate and sodium nitrite. These drugs in doses of 0.0004 and 0.06 Gm., respectively, were administered at frequent intervals at the first appearance of prodromal symptoms. Two attacks appeared to have been aborted in this fashion, but eventually the fevers occurred despite the two compounds. Finally, the effect of sodium diphenylhydantoinate was tried. Accordingly, that drug was administered in doses of 0.1 Gm. four times a day. The patient had one more febrile attack two days after the institution of this therapy. In that attack, August 8, the rectal temperature rose to 39 C. (102.2 F.). From then on he was free of attacks until July 25, 1941. The apparent success of this drug, which is used almost exclusively in the treatment of epilepsy, suggested that this syndrome might be more closely related to "epilepsy" than to migraine. Sudden



Changes in the rectal temperature, pulse and number of white cells per cubic centimeter during a typical febrile attack.

withdrawal of the drug, however, after forty-four days of administration failed to induce an attack, although such a sudden withdrawal of anticonvulsant drugs is known to induce convulsive seizures in "epileptic" patients.<sup>17</sup> Other measures which are known to induce seizures in such persons were tried. The patient was kept awake for twenty-four hours, given exhausting mental, manual and physical work to do and fed alcoholic beverages throughout the twenty-four hour period, totaling in alcoholic content 120 cc. of 95 per cent ethyl alcohol. Later for a week his fluid intake was maintained in excess of 6,000 cc. daily. In the midst of this period he was given 1 cc. of solution of posterior pituitary U. S. P. intramuscularly. On the day of injection his urine output fell from 5,000 cc. to 2,500 cc.,

15. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, *A. Research Nerv. & Ment. Dis., Proc.* (1937) **18**: 638, 1938.

16. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache: B. Contrast of Vascular Mechanism in Preheadache and in Headache Phenomena of Migraine, *Arch. Neurol. & Psychiat.* **45**:199 (Feb.) 1941.

17. Dunning, H. S.: Convulsions Following Withdrawal of Sedative Medication, *Internat. Clin.* **3**:255, 1940.

indicating storage of fluid. None of these measures was successful in precipitating a febrile attack. The patient continued free of attacks without any further drug therapy.

The patient was subjected to a careful personality study. His family environment throughout childhood was rather rigid. His father was a strict, quiet and undemonstrative man. It has already been stated that he was subject to sick headaches and bouts of fever. His mother lay constant emphasis on culture and breeding. It was considered bad form at home to display any affection or other emotional reaction. He was conscientious and serious as a boy and extremely sensitive to the opinions of others, especially to disparaging remarks. His parents expected him to excel in his studies, and he did so, nearly always leading his classes. He entered college at the age of 17 but left in his third year to enlist in the Navy shortly before the United States declared war on Germany. He felt superior to other seamen and was distressed by their vulgar speech and manners. He soon earned for himself a commission as ensign, and later one as lieutenant. After the war he returned to college and in a year obtained a degree in engineering.

His past training and experience had inculcated in him high standards of performance, and the idea of failure was intolerable to him. Although he was a good engineer, he never became a business "success." He was unable to adjust his rigid personality to the "give and take" standards of the business world. He had a strict ethical code in business dealings, which in his opinion was frequently offended by unscrupulous tactics in general practice. He asserted, "I am incapable of in any way cultivating friendships with the thought that they may be useful to me in business." He felt insecure in the business world and anxious about his success. At the age of 25 he formed a company with two partners, but he resented strongly every instance in which his opinion was not able to prevail in business discussions. He admits that the venture might have succeeded "if I had been able to subjugate my opinions to those of my associates." The patient frantically redoubled his output of work in order to make his losing venture succeed. At this time he was tense, more anxious than ever and resentful that the whole onus had fallen on his shoulders. His periodic headaches became so severe as to be incapacitating, and it was necessary for him to quit work for a time.

Although he insisted on imposing his standards on other persons, it is interesting that in his personal relations he depended for emotional support on others, while he gave out comparatively little himself. "My friends assume a protective or paternal attitude that I don't particularly object to."

Six months after a disappointing love affair, when he was 27 years old, he met the woman whom he later married. They were both "given to critical analysis" and "sensed a kindredness of spirit." He passionately wished his marriage to be a perfect partnership, so he entered on it cautiously. He was especially anxious that neither his wife's nor his own "individuality" should be encroached on by the union. Accordingly, he drew up a contract which provided that each of them should be a free agent whose behavior was not to be hampered by the conventional restrictions of marriage. They deliberately undertook extramarital connections as "an expression of unhampered individuality to convince us that the verdancy of distant pastures may be somewhat illusory." Their experiences did not appear to affect his wife deeply one way or another. The patient, however, was offended by the experiences despite the fact that they had been at his own instigation. His first febrile episode followed his first extramarital experience, and his second, six weeks later, followed his wife's first experience. From that time on the patient became impotent in his relations with his wife. His general behavior became more compulsive than ever. He kept filed voluminous data and charts of events in his



illness, with meticulous attention to minutiae. The collection and classification of this mass of material became increasingly time-consuming and interfered with the accomplishment of his regular duties. He wrote daily letters to his wife on the typewriter and kept a carbon copy of each, meticulously filed away and clipped to the latest reply.

On examination the patient was alert and friendly. He seemed intensely interested in his illness but not much disturbed by it. He stated, "I have cultivated an impersonal attitude toward my illness." He frequently spoke in the third person or referred to himself as "we." In discussing his past life and personality reactions his manner was circumstantial and pedantic. He put undue stress on the selection of words and when discussing his status used involved medical terminology, at times sacrificing clear meaning for the use of intriguing words. He even occasionally concocted words. One was "frameria," which he said meant literacy and symmetry.

He expressed abnormal fears of large strange dogs, burglars, darkness, fire, bodily injury and a lingering illness. These had persisted since childhood. He avoided conflict with others, physical or mental. He was unhappy in controversial business discussions because he became "rattled and fearful and felt frustrated." Meticulous in his habits, he found it "impossible to slight work." After once undertaking a job he felt that he must carry it through at any cost. He was constantly obsessed by details of a problem and felt compelled to go over each one again and again.

The almost daily interviews necessary to elicit these data gave the patient an excellent opportunity for "mental catharsis." His illness was formulated to him as a functional disorder of the thermoregulatory apparatus in a setting of anxiety, insecurity and resentment precipitated by his two failures, business and marital. These failures were intolerable to him. He accepted this orientation and gained in time a good understanding of his condition. This, together with other less well defined factors, effected in him a marked improvement. At the time of discharge, he felt that his conflicts had been resolved to a large measure and he felt able to face his problems with more serenity. He accepted the inevitable fact that there were certain tasks which he could not do perfectly. In a letter written after he had been home and free of attacks for more than seven months he indicated that he had actually been able to face his life problems with less anxiety and conflict. He had found congenial work of a less intense type than that in which he had been engaged before he came to the hospital. He was employed in a consulting capacity by a large firm. He no longer had the interference of business partners to arouse resentment within him. He felt more secure both in his business and in his domestic relations, and fear of failure was no longer uppermost in his mind.

After a time, however, the work became gradually more intense, and during the phase of accelerated production for national defense the patient undertook the responsibility of designing a machine for the Army in a much shorter time than he was actually able to do. In this setting, after three hundred and fifty-one days free of fever, an anxiety tension state developed, and with it he had two bouts of fever similar to the old episodes. Whether this relapse will reestablish his rhythm of attacks or whether the bouts will constitute isolated occurrences is yet to be demonstrated.

#### COMMENT

It is unfortunate that the patients whose conditions were described in the literature on the subject of psychogenic fever were not subjected to detailed personality study, although in many instances they were

referred to as "neurotic" or "hysterical." Our patient has been studied carefully from the standpoint of the personality and found to fit into the reaction type characterized by obsessive and compulsive behavior. There was a family history of mental illness requiring hospital treatment on the maternal side and of migraine on the paternal side. His early home environment was rigid and uncompromising. His parents relentlessly demanded of him a high standard of performance. They would brook no failure. The patient himself was sensitive to slights, conscientious and insecure when without the approval of others. As a compensation for his essential passive nature with its dependency on others he assumed a kind of dominant attitude which showed itself in his pedantic behavior and in his inflexible life standards. While in school and college, when he had only himself and his books to reckon with, he led his classes and thus was able to feel secure with the approval of others. When he entered the business world, however, his inflexible attitude and rigidly systematized behavior proved a hindrance, and in consequent failures he experienced conflicts and feelings of insecurity. This was the period during which he was nearly incapacitated by his migraine headaches. When later he had to fit marriage into his rigid system of life, he found the task insurmountable. In this setting, during his early married life, the recurrent febrile attacks appeared.

The mechanism responsible for the fever is not clear, but it is possible that the attacks may be due to a vasomotor disturbance akin to that encountered in migraine.<sup>18</sup> This is suggested by the fact that the patient doubtless had migraine headaches and that these recurrent headaches were interrupted during the periods when he was suffering from recurrent fevers. Migraine is known to be a vasomotor disorder,<sup>18</sup> and furthermore, this patient has been shown to have vasomotor disturbances associated with changes in his emotional state by the fact that one can raise the cutaneous temperature of an extremity by suggestion. It is possible that a similar vasomotor change in the thermoregulatory apparatus may be responsible for his bouts of fever.

#### SUMMARY AND CONCLUSIONS

A case is presented in which the patient had suffered for many years with periodic sick headache and for thirteen years with frequently recurrent bouts of fever up to 40 C (104 F.). At intervals during this time he was hospitalized and carefully studied at three large institutions. An infectious, neoplastic or metabolic cause for his fever was never demonstrated, and indeed, the patient did not show loss of weight,

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18. Wolff, H. G.: Personality Features and Reactions of Subjects with Migraine, *Arch. Neurol. & Psychiat.* 37:895 (April) 1937.

debility or other evidence between attacks of being physically ill during or at the end of the thirteen years. Numerous therapeutic measures were ineffective in halting the attacks. After a personality study during which a great many personality disorders were uncovered, he was given an opportunity to ventilate his conflicts and some aid in resolving them. During this regimen his recurrent fevers stopped, and he had neither fever nor headache for nearly a year. Finally, while living in another part of the country where it was no longer possible for us to follow him up closely, the patient suffered a recurrence of his intermittent fevers. This occurred in a setting of unusual tension and anxiety. The fevers are believed to be due to a temporary derangement in the thermoregulatory centers of the brain, possibly of a vascular nature, arising in a setting of anxiety and insecurity in a rigid, compulsive person who has had migraine.

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# Progress in Internal Medicine

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## DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1941

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BOSTON

### THE HEART IN WARTIME, WITH SPECIAL REFERENCE TO NEUROCIRCULATORY ASTHENIA

Nearly every one sensible of the war has felt its impact in some degree. Those within sight and sound of the shock of battle are affected most, but the rest do not escape. In addition to direct injury, disease and starvation, the increase in physical and psychologic stress and strain will most assuredly result in increased wear and tear on the body, including the cardiovascular system. The hours and the tempo of work will be increased, and older persons will forego, or will be called back from, retirement. There will be many causes and occasions for grief and anxiety. And the wholesale readjustment resulting from war will cause much concern.

Just how this will affect the incidence and aggravation of heart disease will never be known exactly. But already there have been many instances of the development of angina pectoris, congestive failure and myocardial infarction which are attributable to the war. Also of importance may perhaps be the hastening of degenerative processes, such as coronary atherosclerosis, which will eventually result in heart disease. Even if in the case of a single person the effect is slight, it assumes great importance when multiplied by the millions of persons involved. Compensations will probably result in that benefits will come from an increase in the knowledge of nutrition, traumatic heart disease and neurocirculatory asthenia, and the actual incidence of certain diseases associated with overnutrition, especially diabetes and hypertension, is likely to decline.

Neurocirculatory asthenia continues to be the most controversial wartime cardiac problem. There are some physicians who refuse to recognize it as a clinical syndrome. There are others who have found it wise to treat a patient with this condition as an ordinary medical

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From the Cardiac Clinic of the Massachusetts General Hospital.

patient suffering from fatigue without referring him either to a cardiologist or to a psychiatrist and in this way to avoid overemphasis either of the cardiac or of the mental state in the patient's mind. But by whatever name their condition is called and no matter what the emphasis, soldiers who display the symptoms commonly referred to as effort syndrome (England) or neurocirculatory asthenia (United States) constitute one of the important wartime medical problems. The small incidence of this disorder in the United States Army recruits is grossly misleading; potential cases are not recognized.

Wittkower, Rodger and Wilson<sup>1</sup> have made a careful study of 50 unselected soldiers aged 20 to 54 with clearcut effort syndrome. In their civil life 15 were sedentary workers and 35 were manual laborers. It is significant that no fewer than 29 had noticed their first symptoms in civil life, 10 during noncombatant service abroad, 4 after fighting experiences and 1 while in a hospital. After a thorough cardiologic investigation the patients were submitted to a three to six hour psychologic examination covering their whole life history.

Wittkower and his associates found that breathlessness was universally experienced and was the presenting symptom in 21 of their 50 patients and that dizziness, cardiac pain, palpitation, headache, nervousness, sleeplessness, undue sweating, tremor, fatigue while at rest, indigestion, nightmares, cramps, numbness, faintness, constipation and blurring of sight followed in that order. The chief cardiac symptoms, dyspnea, pain, palpitation and fatigue, were usually complained of only after the patient had made some slight effort, but in a few cases these symptoms were present when the patient was at rest.

As a result of the psychologic examination Wittkower and associates were enabled to detect a significant frequency of the following personality types:

Group 1. This group was made up of 20 men characterized by an unusually keen sense of duty and by a rigid and deep morality. As children, the majority had been serious minded, had worked rather than played in their spare time and had had an undue sense of obligation. They were obedient to the point of submissiveness, never told lies and felt unduly guilty about minor lapses. They were poor leaders, did not get into fights and were poorly poised. Nearly all were retarded in their sexual development and were shy in the presence of girls. In their occupations they were industrious and efficient, with perfectionistic tendencies. They avoided the minor indulgences of life; 12 of the 20 were teetotallers, 6 were moderate drinkers and only 1 drank excessively. They had little interest in sexual matters, and many were religious.

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1. Wittkower, E.; Rodger, T. F., and Wilson, A. T. M.: Effort Syndrome, *Lancet* 1:531, 1941.

Group 2. The 11 members of this group were similar to those in group 1 in their overconscientiousness but were more aggressive. Most of them had had an unhappy childhood. Feelings of inferiority were often concealed by a strong desire for independence, by overweening ambition or by a compensatory self-assertive, self-righteous attitude. Later in life their ambitious drive qualified them as efficient workers, but when faced with frustration, they tended to be resigned grouchers rather than open rebels.

Group 3. This group comprised 3 men whose lifelong aggressiveness had arisen in childhood under circumstances similar to those which had produced the grouching resentment of the men in group 2. They were open rebels and had repeatedly been in trouble.

Group 4. This group consisted of 12 men with inferior physique combined with emotional and instinctual immaturity. They were delicate as children, and 8 of the 12 were unfit for games. They sought protection rather than fight their own battles. Their feelings of inadequacy made them shy and retiring. They put forth considerable effort in their occupations but often failed. On joining the service they suffered unduly from the separation from family and often broke down during training.

Group 5. This consisted of a well defined group of 4 soldiers who lacked the severe sense of duty found in the others and who were described as "quitters." They were physically and psychologically inferior and had "apparently given up the struggle for existence before it had properly started."

Wittkower and his associates then considered the predisposing and precipitating factors. They found evidence of life-long physical inferiority in 15 of the 50 patients, and 18 gave a long history of nervousness and of breakdown prior to the onset of effort syndrome characterized by anxiety, restlessness and severe phobias. Possible precipitating factors were found to be emotional strain (34), physical strain (23), febrile illness (21), abuse of nicotine (5), accident (4) and gas poisoning (1). An analysis of the various types of acute or chronic emotional disturbances (in 34 of the 50 patients) showed marked variation in the five personality groups. With respect to causation the fundamental importance of emotional factors is stressed, but the authors point out that this would be incomplete unless the various other factors encountered were taken into account. They illustrate the difficult and complex nature of the causation of effort syndrome with 2 case reports. They conclude that the only constant factor in determining the occurrence of effort syndrome is the preexistence of a "character" disorder, and among the precipitating factors emotional disturbances were the commonest.

Wittkower, Rodger and Wilson's contribution was intended "to assess the relative significance of the various etiological factors encountered." This assessment was made. That they "encountered" all of the significant etiologic factors cannot be proved, and the authors express themselves cautiously with respect to causation and stress its complex nature. Some of the uncertainty rests in the fact that it is difficult to prove the correctness of a psychiatric opinion. Psychiatrists readily discover character disorders; they seem quick to regard as expressions of abnormality those very traits which have so long been considered virtues. It seems to us that the five groups can be broken down into two main groups with three subdivisions in the first and two in the second. It is not surprising that Wittkower and his associates found none of their 50 patients to be emotionally well adjusted, and this fact alone cannot be used to prove a common causation of the effort syndrome. On the other hand, it does appear that the symptoms in some, if not a majority, of their particular patients could best be explained on the basis of emotional factors. It is probable that their group of patients does not represent the total experience of this disorder.

Jones and Lewis<sup>2</sup> have reported an interesting study on more than 200 soldiers who were admitted to an emergency hospital during a twelve month period with conditions given the diagnosis of effort syndrome. In their own words,

The inquiry has been directed to the phenomena; the mechanisms at work in producing them; the external (environmental) causes, remote or recent, which have set these mechanisms in action; and the internal (constitutional) causes which have enabled external causes to act thus. Prognosis and treatment have also been considered. Physiological and psychological data, collected in the course of a more restricted and detailed investigation, are not included here.

In discussing the "phenomena" Jones and Lewis point out that the physical phenomena of effort syndrome have often been fully described and that they have nothing to add, but that the subjective or obviously psychologic phenomena have received little attention. They inquired into the mood and outlook in each of their patients and found that 76 per cent had conscious fear accompanying their symptoms at times and that 72 per cent had attacks while at rest corresponding to the familiar anxiety attack. They found that hypochondriacal phenomena were not uncommon. Fifty-three per cent of the patients were unduly preoccupied with their symptoms, and 64 per cent expressed the belief that they had some disease of the heart.

The authors state:

The mechanisms can be seen physiologically as those of the autonomic system, psychologically as those of emotional expression; this familiar dualist attitude is

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2. Jones, M., and Lewis, A.: Effort Syndrome, *Lancet* 1:813, 1941.

pragmatically justifiable, though the two types or mechanisms can more properly be regarded as two aspects of the same complex happening, each capable of more or less separate and independent activation. Thus fear, as a subjective experience, will as a rule be accompanied by somatic (autonomic) manifestations—sweating, goose-flesh and dry mouth—but fear may be experienced without these physical signs, and some at any rate of these physical signs may be exhibited (for instance, under the influence of drugs) without the subject feeling the same quality of emotion. As to their prevailing mood, 50% of the men were depressed and over 70% showed evidence of anxiety. . . .

It is difficult to describe the psychological mechanisms (as apart from the causes) whereby symptoms are produced. A mechanism implies a fixity of performance, no matter how it is set going or where it is occurring, which is difficult to distinguish in the details of individual psychological behaviour, the nearest approach to it being evident in the development of habits, or so-called complex conditioning. There are at present several psychological theories—for example, the Pavlov theory of conditioned reflexes and the various hormic and libidinal theories of dynamic psychology—in terms of which the mechanism of symptom formation in these patients can be described, but such alternative explanations, equally plausible and equally disputable, are rightly suspect.

There is, moreover, no such regularity in the psychological as in the physical phenomena, since by definition certain physiological phenomena, such as breathlessness, must be present, and the physical apparatus subserving these phenomena must therefore be in action, whereas there is no word of explicit psychological phenomena in the definition. Consequently the term includes patients with anxiety and depression of which they are aware, as well as those who are not conscious of any such feeling; patients who are hysterically keeping up and fostering their symptoms, along with others who hypochondriacally fear theirs; some whose symptoms are physiogenic, as after severe influenza; and some who have no symptoms that cannot be interpreted as plain fright. There is a constant temptation to single out one of these groups and call it true effort syndrome. Actually the problem is not that of effort syndrome but of anxiety neurosis, hysteria, hypochondriasis, post-influenzal fatigue and other states which are all lumped together under this umbrella; and the mechanism is as little or as much known as the pathology of these familiar conditions. We have not found anything peculiar to effort syndrome in the psychopathology of the cases seen here. Studies of the inter-relation of the psychological and physiological phenomena are more to the point, as are studies of the psychological aspect of causation, next to be discussed.

Jones and Lewis then turn to a discussion of external and internal causes. Among the immediate external causes (army life) work or effort was less significant than they had expected it to be. Only 47 per cent of the entire group reported that the work they were doing when their symptoms began was heavier than that to which they were accustomed. Other immediate factors were exhaustion, infection, lack of sleep, separation from family, financial worries, etc. Almost equally important were remote external causes, such as psychologic traumas in childhood and parents with similar symptoms. With respect to internal causes the authors found that soldiers with effort syndrome are not, as a group, more asthenic in build than healthy soldiers and that they have a normal distribution of intelligence. However, they found a study of "function"



more enlightening. Fifty per cent of their patients had symptoms of vegetative disorder, such as breathlessness, palpitation, excessive sweating or diarrhea on slight provocation of an emotional sort. Thirty-eight per cent found it difficult or impossible to wear a gas mask, as it made them feel they were choking and breathless. Forty per cent had not played any games, and only 25 per cent had fairly good athletic records. Half of the men had shown definite neurotic traits and two thirds a more or less pronounced anomaly of personality. In discussing the nature of the disorder, Jones and Lewis state:

The evidence is that effort syndrome is not a homogeneous group from any clinical standpoint, though administratively and practically there are excellent reasons for delimiting it. The syndrome is, however, in its setting, causes and form, a neurotic one. This is not to say that it is mainly a psychogenic disorder. Neurosis, like all mental disorders, can be in considerable measure physiogenic (as postencephalitic obsessional neurosis, postinfective neurasthenia and post-concussional personality disorder illustrate), but it does have to exhibit disturbances of function at a high level of integration—i. e., psychological disturbances—and its symptoms must not be such as can be properly attributed to definite and recognisable organic disease. In this sense effort syndrome is a neurosis. Such a classification does not prejudge the issue of what physiological mechanisms are at work nor indicate that psychological treatment is necessarily called for in all cases. A neurosis is a disorder of the patient, not of his disembodied mind only, or of his mindless body only, if such things can be conceived of. In a neurosis, physiological phenomena, either constitutional or temporary and reversible, will occur along with more conspicuous psychological ones. This is true of all illnesses that can be classified as mental disorders, of whatever degree or type—neuroses and psychoses, physiogenic and psychogenic. The distinction is only one of convenience at bottom.

We have therefore not been satisfied with effort syndrome as a diagnosis, but have classified the cases (100 successive admissions) as follows: anxiety state, acute 17%, chronic 14%; depression 12%; psychopathic personality 18%; hysteria 11%; postinfective 11%; hyperventilation tetany 1%; organic disease 11%; high-grade mental defect 4%; schizophrenia 1%.

Treatment consisted of graduated exercises, systematic occupation and psychotherapy. The last-named treatment was not different from that given to other neurotic patients. The prognosis for the group was only fairly good. About 20 per cent of the patients were apparently cured and returned to the army for full duty; a similar percentage were discharged from the army as unfit. The remaining 60 per cent were returned to the army for light duty. A follow-up study of a large sample of those returned to the army revealed that a third did well, a quarter did moderately well and the remainder had to be discharged as unfit.

Jones and Lewis agree in a broad way with Wittkower and associates that effort syndrome is essentially a mental disorder. This conclusion certainly seems justified from the data they present. This does not remove the possibility that a more adequate explanation for the symptomatology of effort may be found.

Wood<sup>3</sup> has approached the problem of neurocirculatory asthenia (or Da Costa's syndrome, the term for which he states a preference) from a somewhat different point of view than Wittkower and associates<sup>1</sup> and Jones and Lewis<sup>2</sup> but has reached the same general conclusion after close personal contact with 300 patients.

He immediately challenges the observation of Lewis that the symptoms are often no more than exaggerated manifestations of the healthy responses to effort. He compares the symptoms as found in 200 of his patients with those in 50 healthy subjects after exercise and concludes that a different mechanism probably determines the symptoms in the two instances. On the other hand, a comparison of the symptoms and signs of Da Costa's syndrome with those produced in normal persons by some of the unpleasant emotions or in patients with psychoneurosis reveals a great similarity.

Wood then reports his critical observations on the mechanism of the somatic manifestations and attempts to show that the chief symptoms and signs of Da Costa's syndrome are directly or indirectly the result of a neurosis and are not the expressions of an abnormal physiologic response to effort.

A careful study was made of the cause and site of origin of the pain in the chest in selected patients. It was shown that tenderness and pain in 11 patients was abolished after the local injection of procaine hydrochloride into the intercostal muscle. Cutaneous anesthesia was never obtained, showing that the intercostal nerve was not blocked. It was logically concluded that the pain was of local origin and not referred from the heart or elsewhere. It was further shown that inframammary pain on the left side was usually associated with poor movements of the diaphragm and with poor thoracic expansion and that sometimes it was obviously the result of muscular strain. Wood concludes this section as follows:

Left inframammary pain arises in local muscular or fibrous tissue; it may be due to fatigue or strain of certain muscular attachments involved in such actions as cranking a lorry or lifting a heavy weight; to incessant minimum trauma from the overacting heart of cardiac neurosis; it is predisposed to by poor physique in Da Costa's syndrome; it is maintained and exaggerated by the belief that it arises in the heart. Several of these factors may operate together.

Other signs and symptoms were analyzed in a similar fashion, and evidence is given in support of the contention that they are chiefly related to anxiety. Of particular interest is the discussion of breathlessness and hyperventilation. Wood believes that the most probable

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3. Wood, P.: Da Costa's Syndrome (or Effort Syndrome), *Brit. M. J.* **1**: 767 and 806, 1941; Aetiology of Da Costa's Syndrome, *ibid.* **1**:845, 1941.

explanation is that the stimulus is emotional. With regard to the "hyperventilation theory" he concludes:

The total evidence indicates that hyperventilation cannot be held responsible for the symptoms and signs of Da Costa's syndrome, neither by causing tissue alkalosis nor by interfering with the circulation; but, apart from rare organic causes, merely one mechanism by which psychosomatic manifestations are produced. It is commonest in the hysteric.

Thus Wood, having reached the conclusion that the signs and symptoms of Da Costa's syndrome are produced by central stimulation, turns to a consideration of the real nature of the disorder, namely, the origin of the central stimulation. By careful analysis of case histories he shows that the central stimulus is emotional and is commonly the result of fear. He states:

The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning, and hysteria.

Wood finally urges that the diagnosis of "effort syndrome" be dropped, as a proper psychiatric diagnosis is nearly always available.

In our opinion Wood's paper is likely to stand out as one of the most important contributions on the disorder which we now call effort syndrome or neurocirculatory asthenia. This is not so much because of his statement that it is a functional disorder—most observers are already of this opinion—but because he has given good proof for this belief and has pointed out a plausible mechanism. There is little doubt that his interpretation is the correct one for a majority of cases, and it is supported by the findings of Wittkower and associates<sup>1</sup> and of Jones and Wilson,<sup>2</sup> who share the same general opinion.

Parkinson<sup>4</sup> discusses effort syndrome from a more general standpoint. He fully appreciates the importance of the emotional factors but warns against too readily accepting the opinion that it is simply a psychoneurosis and says:

It is not certain how far this definition will carry us, because the term can be so readily applied to any form of ill-health which is imperfectly understood and unaccompanied by organic signs. After all, psychological variations and faults in healthy people are common enough. It could only be a bar to medical progress if psychoneurosis (or psychosomatic disease) remained a label and became a dumping-ground for most unexplained illness, much as did "neurasthenia" in the past. It is still to be decided how far psychotherapy is rational and effective treatment; besides, an explanation for the predominance of circulatory symptoms, the relation of effort, and the relative uniformity of the clinical picture is not yet forthcoming. Certainly the time is ripe not only for psychological but for other investigations, as it would appear that autonomic nervous, endocrine, respiratory,

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4. Parkinson, J.: Effort Syndrome in Soldiers, *Brit. M. J.* 1:545, 1941.

and metabolic factors may also operate in effort syndrome, and will also engage the attention of the physician seeking a wider conception of its essential features. Doubtless this expanded approach has much to commend it, and will deepen and broaden our vision of what is at present obscure in the rationale of effort syndrome.

White<sup>5</sup> has discussed the problem of heart disease in soldiers. He first traces the development of present knowledge in this regard and points out that a considerable advance has been made in the last two decades in three important respects: (1) the rejection as new recruits of men with important cardiovascular lesions; (2) the early recognition of disabling cardiac conditions in the Army itself, and (3) the adoption of measures to protect soldiers from some of the causes of heart disease, particularly syphilis and rheumatism.

In discussing the problems concerning the soldier and his heart for the future he states:

In the first place, physicians must try to hold the great gains that have been made in the last generation; this is not hard to do in time of peace but undoubtedly more difficult under the stress and strain of rapid mobilization and war, when large numbers of new recruits must be examined and enlisted. Some preparedness can be effected by careful universal periodic examination of the male population of military age in time of peace. This doubtless will some day be a routine public and private health measure.

The important specific problems are: first, to learn far better than is now known the range of the normal heart as to size, sounds, action, roentgen picture and electrocardiogram; second, to decide what minor abnormalities may be safely passed for military service; third, to detect at their very beginning lesions of the heart and aorta, especially acute rheumatism and syphilitic aortitis; fourth, to decide what newly acquired lesions or symptoms and signs are compatible with military life and in what capacity, and, finally, to study further the two chief problems of the army of the present day which are associated with cardiac lesions or symptoms, namely, coronary disease and severe neurocirculatory asthenia, in order to try to prevent or to minimize these conditions or at least to recognize them early, so that they may be avoided in new recruits or made a basis for discharge for disability of soldiers already in service.

#### PHYSIOLOGY OF RESPIRATION

The functions of the circulatory and the respiratory system are so intimately connected that a brief summary of certain of the recent advances in respiratory physiology seems not out of place here. Some of the newer observations are of great practical significance and have not yet been brought sufficiently to the attention of those engaged in the clinical practice of medicine. For a fuller description than is here given the reader is referred to Schmidt and Comroe's excellent review.<sup>6</sup>

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5. White, P. D.: *The Soldier and His Heart*, War Med. 1:158 (March) 1941.

6. Schmidt, C. F., and Comroe, J. H., Jr.: *Respiration*, in Luck, J. M., and Hall, V. E.: *Annual Review of Physiology*, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 151.

The physiology of respiration is logically divided into "external" and "internal" respiration. The remarks which follow are chiefly concerned with external respiration, which deals with the interchange of gases between the atmosphere and the lung and between the lung and the blood. Internal respiration deals more intimately with the actual process of tissue respiration.

Breathing is the most important physiologic function, under both voluntary and involuntary control. Ordinarily, it is not a wilful act but is regulated automatically through reflex and chemical channels, in accordance with the metabolic requirements of the body. Breathing is normally adjusted to maintain a fairly constant composition of the alveolar air, and it is alveolar air and not atmospheric air with which the body remains in gaseous equilibrium. Alveolar air contains approximately 14 per cent oxygen and 6 per cent carbon dioxide. If the respirations are abnormally depressed, the percentage of oxygen in alveolar air decreases and the percentage of carbon dioxide increases, both changes being undesirable. If the respirations are abnormally increased (hyperventilation), the percentage of oxygen increases, which is not undesirable, but the decrease in carbon dioxide may provoke undesirable symptoms.

*The Respiratory Center.*—It has long been customary to think of the respiratory center as a small discrete structure located in the medulla. However, the evidence cited by Schmidt and Comroe<sup>6</sup> makes it seem certain that instead of a compact center there are many inspiratory and expiratory "spots"<sup>7</sup> scattered bilaterally in the gray matter of the ventral reticular formation of the medulla overlying the upper four fifths of the inferior olive and probably an additional expiratory "center" in the upper part of the pons.

Normal rhythmic respiration probably depends on periodic inhibition of the inspiratory neurons by nerve impulses aroused by the inspiratory act. There is not entire agreement with regard to the reciprocal innervation between the inspiratory and the expiratory neurons, but the former are apparently inhibited either by efferent impulses from the expiratory center in the pons or by afferent impulses carried by the vagi.

In discussing the interrelations of chemical and reflex stimuli in the adjustments of the pulmonary ventilation, Schmidt and Comroe emphasize the dominance of the reflex factor and state that in their opinion

. . . the time has come to reverse the traditional attitude and to look upon the changes in the chemical stimulus in the blood occurring under ordinary physiological as well as most pathological conditions as results rather than causes of changes in pulmonary ventilation.

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7. Pitts, R. F.: The Differentiation of Respiratory Centers, *Am. J. Physiol.* 134:192, 1941.

With respect to chemical stimuli there is increasing evidence that normally carbon dioxide is the chief, if not the only, chemical stimulus to the center controlling respiration. It is doubtful if changes in  $p_{H_2}$  have a direct effect on the center.

Respiratory reflexes may arise as a result of pressure changes in the carotid sinus and aortic arch and, what is more important, as a result of stimulation of the chemoreceptors in the carotid and aortic bodies. There is evidence that the chemoreceptors are not an important factor in the control of normal respiration by carbon dioxide because the respiratory center is much more sensitive to carbon dioxide. However, change in  $p_{H_2}$ , anoxemia and certain drugs act as relatively strong stimulants to the chemoreceptors, and their action on the center is weak or even depressant.

*Some Clinical Considerations.*—Muscular Exercise: The increase in respiration as a result of muscular exercise has usually been regarded as being due either to increased chemical stimulation of the respiratory center or to an increased sensitivity (to chemical stimuli) of the center. Recent observations, especially those of Neilsen,<sup>8</sup> have convincingly shown that the hyperpnea of muscular exercise is far greater than it should be if it were due to an increase in carbon dioxide, change in  $p_{H_2}$  or lowered arterial oxygen saturation. The inference to be made is that some reflex factor is concerned, and there is some evidence that such reflexes do exist and that they probably arise from the muscles and lungs.

The Dyspnea of Heart Failure: Much the same type of experimental evidence, as was already mentioned with reference to muscular exercise, has led to the conclusion that the dyspnea associated with heart failure is largely due to reflex stimulation resulting from congestion of blood in the pulmonary circuit. However, in some instances at least, the decrease in cardiac output and the decrease in cerebral blood flow are important factors.

The Hyperpnea of Anoxemia: This has been clearly shown to be due to reflex stimulation by way of the chemoreceptors in the carotid and aortic bodies. Moderate oxygen lack has practically no effect on the respiratory center and with greater lack the activity of this center is depressed, not stimulated. On the contrary, anoxemia acts as a strong stimulant to the chemoreceptors, and respiration is greatly augmented through a reflex mechanism. A depressant action is not observed until a profound degree of anoxemia is reached.

Cheyne-Stokes Respiration: This phenomenon is usually associated with conditions causing depression of the respiratory center, but the

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8. Nielsen, M.: Die Respirationsarbeit bei Körperruhe und bei Muskelarbeit, Skandinav. Arch. f. Physiol. **74**:299, 1936.

stimulant action of anoxemia on the peripheral chemoreceptors persists and contributes in an important way. Thus, when respirations are decreased or abolished as a result of depression of the respiratory center, the arterial oxygen saturation falls. Despite some degree of depression of the chemoreceptors, the oxygen lack finally becomes a sufficiently powerful stimulus and respiration is reflexly increased. This serves to increase the arterial oxygen saturation until the degree of anoxemia is no longer sufficient to stimulate the chemoreceptors and apnea results. Thus one cycle is completed, and another cycle of alternate hyperpnea and dyspnea begins.

**Anesthesia and Depression of the Respiratory Center:** A few years ago Marshall and Rosenfeld<sup>9</sup> pointed out that if the respiratory center was sufficiently depressed in animals as a result of barbiturate anesthesia, respirations might be maintained by the stimulant action of anoxemia on the chemoreceptors in the carotid and aortic bodies, and if conditions were just right, the administration of oxygen would reduce the stimulus and lead to respiratory arrest. That this may be the mechanism of certain deaths in human beings is likely. Beecher and Moyer<sup>10</sup> in their studies on the mechanisms of respiratory failure in dogs under evipal sodium (sodium C-C-cyclohexylenyl-N-methylbarbiturate) and pentothal sodium anesthesia have also shown that over a wide range of anesthesia oxygen lack (anoxemia) causes a great increase in pulmonary ventilation. This is due entirely to stimulation via the carotid and aortic bodies, which tends to mask the depression of the respiratory center. Under these circumstances, if the arterial oxygen saturation is sufficiently increased, the carotid and aortic bodies are no longer adequately stimulated. Respirations are slowed, and carbon dioxide is allowed to accumulate in the blood and tissues. The center has lost much of its ability to respond to carbon dioxide and will be further depressed by high concentrations. Respirations finally fail. The clinical implications are obvious, with respect both to the judgment needed in using barbiturates as anesthetics and to the danger of increasing the oxygen concentration of the inspired air when the respiratory center has been depressed.

**Carbon Monoxide Poisoning:** A comparison of the effects of acute carbon monoxide poisoning and anoxemia in human beings<sup>11</sup> affords

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9. Marshall, E. K., Jr., and Rosenfeld, M.: Depression of Respiration by Oxygen, *J. Pharmacol. & Exper. Therap.* **57**:437, 1936.

10. Beecher, H. K., and Moyer, C. A.: Mechanisms of Respiratory Failure Under Barbiturate Anesthesia (Evipal, Pentothal), *J. Clin. Investigation* **20**:549, 1941.

11. (a) Asmussen, E., and Chiodi, H.: The Effect of Hypoxemia on Ventilation and Circulation in Man, *Am. J. Physiol.* **132**:426, 1941. (b) Chiodi, H.; Dill, D. B.; Consolazio, F., and Horvath, S. M.: Respiratory and Circulatory Responses to Acute Carbon Monoxide Poisoning, *ibid.* **134**:683, 1941.

considerable insight into the factors controlling respiration and circulation. It is shown that there is a markedly different respiratory and circulatory response to the two forms of hypoxemia even when the available oxygen in the arterial blood is the same. The reason for this is that the carotid and aortic bodies are stimulated by a decrease in oxygen tension of the arterial blood and not by a decrease in oxygen content, at least of moderate degree. In acute carbon monoxide poisoning, the oxygen content of the arterial blood is reduced but the tension is relatively little affected. In this circumstance hyperventilation does not occur; the cardiac output is not increased, but the pulse rate is raised. On the other hand, anoxemia resulting from oxygen lack decreases the oxygen tension as well as the content of the arterial blood. This leads to hyperventilation, an increase in cardiac output and an increase in pulse rate.

**Carbon Dioxide Transportation:** The absorption of carbon dioxide by the blood in the tissues and its evolution in the lungs proceeds at a much faster rate (seventy-five-fold) than would be true according to the speeds of uncatalyzed chemical reactions involved. The limiting factor (i. e., the slowest step) is the reaction  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3$ , and it has been shown that this is greatly hastened by the enzyme "carbonic anhydrase." Now it has recently been shown<sup>12</sup> that sulfanilamide strongly inhibits the action of this enzyme, and the question arose as to whether this drug would lead to retention of carbon dioxide and its consequent serious disturbances. The danger however, is apparent only in exhaustive exercise,<sup>13</sup> chiefly because the available amount of carbonic anhydrase is many times that of body needs and also because a part of the carbon dioxide transported will rapidly combine with hemoglobin (forming carbbemoglobin) with the aid of a catalyst.

#### THE MEASUREMENT OF BLOOD PRESSURE

Recent studies, previously reviewed,<sup>14</sup> on the range of normal blood pressure led to the conclusion that the upper limit is around 120 mm. of mercury systolic and 80 mm. diastolic and the normal fluctuations, determined by repeated observations, are usually not over 10 mm. It was further stated that the lower limit of normal blood pressure is around 90 mm. systolic and 55 mm. diastolic. The commonly accepted

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12. Mann, T., and Keilin, D.: Sulphanilamide as Specific Inhibitor of Carbonic Anhydrase, *Nature*, London **146**:164, 1940.

13. Roughton, F. J. W.; Dill, D. B.; Darling, R. C.; Graybiel, A.; Knehr, C. A., and Talbott, J. H.: Some Effects of Sulfanilamide on Man at Rest and During Exercise, *Am. J. Physiol.* **135**:77, 1941.

14. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1939, *Arch. Int. Med.* **65**:1053 (May) 1940.



view of a positive relation between hypertension and body build has also been statistically confirmed; thus, in a random group of hypertensive subjects there will be nearly three times as many who are overweight as ones who are underweight. The recent trend has been, therefore, to revise downward the criteria for normal blood pressures and to narrow the borderland between the normal and the abnormal. The recent recommendations of the American Heart Association with regard to the technic of blood pressure determination were made with the hope that by standardizing the instruments and the technic, the difference in measurement among examinees would be reduced.

This whole question of greater accuracy in the determination of blood pressure and the sharper definition of normal blood pressure gives particular point and application to the observations of Rogan and Bardley.<sup>15</sup> They undertook to test the accuracy of clinical measurements of blood pressure by a comparison of readings obtained simultaneously by direct (intra-arterial) and indirect (auscultatory) measurement.

With respect to systolic pressure Rogan and Bardley found that the agreement between the direct and the indirect measurement was affected both by the size of the subject's arm and by the contour of the pulse wave. They found that when the pulse wave was of an "empty, peaked" type, the auscultatory reading tended to be too low, whereas with a relatively full pulse there was good agreement between intra-arterial and auscultatory readings. Much more important, however, was the size of the arm. The auscultatory measurements of systolic pressure are usually too low in subjects with small arms and too high in subjects with large arms. In occasional subjects they found the auscultatory measurements to be grossly inaccurate (30 mm. above or below the intra-arterial pressure), but when the subjects with aortic insufficiency and those with upper arms greater than 35 cm. or less than 24 cm. in circumference were excluded, the auscultatory readings were within  $\pm 10$  mm. of the intra-arterial pressure in 83 per cent of the comparisons. From this they conclude that false diagnoses of arterial hypertension are likely to be made in large or obese persons and false diagnoses of hypotension only in small or emaciated persons. In some obese subjects it was found that the substitution of a wide (20 cm.) blood pressure cuff for the standard (13 cm.) cuff afforded more accurate auscultatory measurements both of systolic and of diastolic pressure, but in most subjects the wide cuff yielded measurements which were too low.

With respect to diastolic pressure the auscultatory estimates were found to be usually too high, the mean deviation being  $+8$  mm. of mer-

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15. Rogan, C., and Bardley, J., III: The Accuracy of Clinical Measurements of Arterial Blood Pressure, with a Note on the Auscultatory Gap, *Bull. Johns Hopkins Hosp.* 69:504, 1941.

cury in 101 comparisons (excluding the subjects with aortic insufficiency). The positive deviation increased with increasing size of arm and was of an order of approximately 3 mm. for each 1 cm. increase in arm circumference. As was to be expected in some instances of aortic regurgitation, the auscultatory measurement of diastolic pressure was much too low.

#### AUSCULTATION

Rappaport and Sprague<sup>16</sup> have presented an important analysis of the characteristics of human hearing which are related to auscultation. This material is followed by a description of cardiac sounds, murmurs and noncardiac chest sounds from a physical point of view. A theoretic analysis of the action of the acoustic stethoscope and various chest pieces (open bell and diaphragm bell types) is made and verified by experiment. For practical purposes it is shown that in auscultating the heart both an open bell and a diaphragm bell may be used to advantage. They point out that the important consideration with respect to the open bell is to keep its internal volume at a minimum and have it so shaped that it will not too readily fill with flesh when applied to a patient's chest. In the case of the diaphragm bell the air space should be small in order to obtain maximum efficiency. The tubing should be as short as possible.

An instrument is also described (including the underlying theoretic principles) which is capable of amplifying the auscultatory sounds without altering their character and which simultaneously registers a phonocardiogram, an electrocardiogram and a sphygmogram.

The authors show that when a patient is auscultated by the usual stethoscope, the observer definitely does not hear the cardiac sound vibrations as they actually exist at the source, because of three major forms of modification, namely:

1. The heart sounds are modified in their path of travel from the source to the surface of the chest by intervening tissue.
2. The vibrations that reach the surface of the chest are further modified by the stethoscope and the type of chest piece employed.
3. The human hearing mechanism (that is, the ear, the nervous pathways and the brain) additionally modifies the heart sound vibrations.

The study of acoustics as related to auscultation, therefore, deals with the vibrations or disturbances set up in the chest and their transmission through the structures of the chest, as well as through the stethoscope—with resulting auditory perceptions.

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16. Rappaport, M. B., and Sprague, H. B.: *Physiologic and Physical Laws That Govern Auscultation, and Their Clinical Application*, *Am. Heart J.* **21**:257, 1941.

In phonocardiography certain standards must be decided on and faithfully adhered to. The authors have suggested phonocardiographic standards based directly on the stages of sound modification encountered in ordinary auscultation. Thus, three distinct types of phonocardiographic registration are considered: linear, stethoscopic and logarithmic.

Linear phonocardiography registers graphically the mechanical vibrations set up by cardiac action as they exist on the surface of the patient's chest—that is, the deviation of the recording galvanometer beam is proportional to the intensity of the vibration at the surface of the chest. The stethoscopic system of phonocardiographic registration does not register the cardiac sound vibrations as they exist on the surface of the patient's chest but as they are presented to the ears of an observer by an average acoustic stethoscope. The logarithmic phonocardiogram is a graphic representation of the cardiac sound vibrations as they are actually heard or perceived by an average observer of normal hearing when an average acoustic stethoscope is used. That is, the modifications of the stethoscope plus those of human hearing are taken into consideration.

According to the authors, an acceptable phonocardiographic instrument must be capable of linear, stethoscopic and logarithmic registration, as each system supplies certain information which the others cannot supply. An understanding by a physician of the underlying phonocardiographic principles described in this investigation is also considered by the authors to be essential to the interpretation of phonocardiograms.

#### ELECTROCARDIOGRAPHY

Hoff and Nahum and their associates<sup>17</sup> have reported their interesting observations on the genesis of the normal and the abnormal electrocardiogram in experimental animals. They obtained curves after cooling and warming the heart and after extinguishing electrical activity over various portions of the epicardium by means of potassium chloride.

They found that curves obtained after extinction of the electrical activity over one ventricle resembled those derived directly from the surface of the other ventricle. Such curves were called dextrocardiograms and levocardiograms. The dextrocardiogram is mainly upright in the three limb leads, and the levocardiogram is mainly inverted. The

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17. (a) Nahum, L. H.; Hoff, H. E., and Kaufman, W.: Formation of the R Complex of the Electrocardiogram, *Am. J. Physiol.* **134**:384, 1941; (b) The Nature of Leads I and III of the Electrocardiogram, *ibid.* **134**:390, 1941; (c) Configuration of Anterior and Posterior Septal Extrasystoles in the Standard Leads of the Electrocardiogram, *ibid.* **134**:398, 1941; (d) Influence of Right and Left Ventricles on the Electrocardiogram, *ibid.* **131**:687, 1941; (e) The Significance of Displacement of the RS-T Segment, *ibid.* **131**:693, 1941. (f) Hoff, H. E., and Nahum, L. H.: The Factors Determining the Direction of the T Wave: The Effect of Heat and Cold upon the Dextro- and Levocardiogram, *ibid.* **131**:700, 1941.

electrocardiogram was found to be the algebraic sum of the dextrocardiogram and the levocardiogram.

It was observed that when the left ventricle alone was injured dextrocardiograms were always obtained and the RS-T segments were elevated in each lead and when the right ventricle was injured only levocardiograms were obtained, with the RS-T segments depressed in all leads. In each instance the greatest displacement of the RS-T interval would be in lead II, because lead II is the algebraic sum of leads I and III. However, when the anterior surface of the heart was injured, thus involving both the right and the left ventricle, the RS-T segment was elevated in lead I (posterior dextrocardiogram) and depressed in lead III (posterior levocardiogram). When the posterior surface of the heart (apex and posterior septal region) was injured, the RS-T interval was depressed in lead I (anterior levocardiogram) and elevated in lead III (anterior dextrocardiogram). In addition to the clinical implications, these results suggested that in the normal heart lead I represents chiefly the interference between the action potentials of the anterior surface of the left ventricle (anterior levocardiogram) and the posterior surface of the right ventricle (posterior dextrocardiogram) and that lead III represents the algebraic sum of the anterior dextrocardiogram and the posterior levocardiogram. Lead II appears to record from the entire heart. This conclusion was supported by studies on the T waves, R waves and extrasystoles now to be described.

Hoff and Nahum and associates found that heating and cooling the right or the left ventricles shortened or lengthened, respectively, the dextrocardiogram or the levocardiogram. They observed that in the dog the dextrocardiogram begins first and ends sooner than the levocardiogram, and consequently the T wave is inverted. When the left ventricle was warmed, the levocardiogram became shorter, and the T wave became upright, whereas if the right ventricle was warmed, the dextrocardiogram was shortened and the T wave became deeply inverted. The opposite effects were produced by cooling. Changes in the amplitude and the direction of the chief initial ventricular deflection were produced and explained in this same manner. They observed:

When the anterior surface of the heart was cooled by a thermal chamber covering portions of both right and left ventricles, oppositely directed T waves appeared as follows: *a*, a prolonged, inverted T wave appeared in lead I, indicating in this lead the influence of a prolonged levocardiogram which could have been derived only from the cooled anterior surface of the left ventricle; *b*, in lead III the T wave was upright and prolonged, indicating the influence in this lead of a prolonged dextrocardiogram which could have been derived only from the anterior surface of the right ventricle. Lead I therefore must have recorded preponderantly from the anterior surface of the left ventricle. The results obtained by warming the anterior surface also showed oppositely directed T waves in leads I and III. In

this case, however,  $T_1$  was upright, indicating curtailment of the anterior dextrocardiogram. This substantiates the hypothesis that the anterior levocardiogram is recorded in lead I, while the anterior dextrocardiogram is recorded in lead III.

When the posterior surface of the heart was warmed, the T waves became inverted in lead I and upright in lead III, whereas after cooling the T wave became upright in lead I and inverted in lead III.

With respect to ventricular premature beats it was found that stimulation of the major portion of the left ventricle resulted in beats showing initial downward deflections in the three leads, while stimulation of the major portion of the right ventricle resulted in beats showing initial upward deflections in the three leads. Premature beats arising from the anterior septum were found to be comparable with ventricular complexes at present interpreted as having right axis deviation (initial deflection down in lead I and up in lead III), while the opposite is true of those arising from the posterior septum.

Hoff and Nahum and their associates indulge in little speculation with regard to how far their results might be used in explaining some of the electrocardiograms obtained on patients. Certainly their methods, especially the use of heat and cold, are not comparable to what might occur in a human being. Also, the levocardiograms and dextrocardiograms they obtained do not resemble in their initial portions (duration and form of QRS) the corresponding portions of true levocardiograms and dextrocardiograms. However, this difference may not vitiate all their conclusions, but any conclusions regarding the representation of various portions of the heart in leads I and III in dogs might not prove to be true for human beings, because the same regions of the heart are not in contact with good conductors.

White, Leach and Foote<sup>18</sup> have called attention to errors in existing methods of measurement of the PR (or PQ) interval and QRS duration in electrocardiograms. The authors point out that it is common practice to accept the longest intervals for PR and QRS as the correct ones in any given record and that the PR interval is usually measured in lead II. However, in occasional records the initial deflections of QRS in leads I and III are of equal amplitude but oppositely directed, thus producing an isoelectric phase in lead II. Thus, in measuring from the beginning of P to R in lead II, a portion of the QRS complex would be added which might be sufficient to make the apparent duration of PR abnormally long. This, in turn, might lead to a false interpretation of serious import, which was exactly the circumstance that first brought the matter

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18. White, P. D.; Leach, C. E., and Foote, S. A.: Errors in Measurement of P-R (P-Q) Interval and QRS Duration in the Electrocardiogram, *Am. Heart J.* **22**:321, 1941.

to the authors' attention. A simple method of avoiding this error is presented, namely, subtracting the figure for the widest QRS wave from that for the longest PS duration (that is, from the beginning of P to the end of S).

It is now well known that a number of factors in addition to heart disease per se may cause lowering or inversion of the T waves of the electrocardiogram. Two recent papers<sup>19</sup> have emphasized the importance of the position of the heart in the thorax as a cause of significant lowering or inversion of the T waves in leads II and III. Most commonly the abnormal appearance of the T waves is observed when the record is obtained while a subject or patient is seated. On changing to the recumbent position, the T wave abnormalities disappear. Evidence is given to support the contention that the T wave changes are not due to anoxemia of the myocardium. The important practical conclusion is evident, namely, that it is often necessary to obtain an electrocardiogram when the patient is recumbent in order properly to evaluate lowering or inversion of the T waves in leads II and III.

Low voltage of the QRS complexes of an electrocardiogram in all of the limb leads has long been considered to be a significant finding. Because most of the electrocardiographic studies have been carried out on patients, in whom low voltage of the QRS complexes is not infrequently observed, this sign was commonly regarded as of pathologic significance. However, as electrocardiograms came to be taken on normal subjects in larger numbers, it was often found that the voltage of QRS in the limb leads was "abnormally" low, and this fact has recently been emphasized by Leach and associates.<sup>20</sup> They analyzed 300 cases in which there was low voltage of the QRS complexes (in one-third in the limb leads alone, in one-third in lead CF<sub>4</sub> alone and in one-third in all four leads) and found that many factors in addition to heart disease were responsible for the low voltage. Their study indicated that the solitary finding of low voltage of the QRS in any or all of the four leads studied is of little or no diagnostic value regarding the presence of heart disease or any other disorder. Bellet and Kershbaum<sup>21</sup> have found that one chest lead alone may yield curves of low voltage. They believe

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19. (a) Scherf, D., and Weissberg, J.: The Alterations of the T-Waves Caused by a Change of Posture, *Am. J. M. Sc.* **201**:693, 1941. (b) White, P. D.; Chamberlain, F. L., and Graybiel, A.: Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart, *Brit. Heart J.* **3**:233, 1941.

20. Leach, C. E.; Reed, W. C., and White, P. D.: Low Voltage of the QRS Waves in the Electrocardiogram with Especial Reference to Lead IV, *Am. Heart J.* **21**:551, 1941.

21. Bellet, S., and Kershbaum, A.: The Significance of Low Voltage of the QRS Complex in Precordial Leads, *Am. Heart J.* **22**:195, 1941.

reliance should not be placed on a single precordial lead for a diagnosis of low voltage and that in addition to leads  $CF_3$ ,  $CF_4$  and  $CF_5$ , leads CB and CR should be taken. Using this criterion, they found that all of 20 patients who had low voltage both in the precordial and in the limb leads showed evidence of myocardial damage.

Weinberg and Katz<sup>22</sup> have called attention to an electrocardiographic pattern following cardiac infarction in which the T waves are simultaneously inverted in leads I, II and III. This pattern was found in about 16 per cent of their cases of a condition proved beyond reasonable doubt to be acute myocardial infarction. In some instances this pattern appeared at the onset, while in others it occurred at some later stage. It may occur as a transitory phenomenon or may remain for some time. The various possible mechanisms responsible for this pattern are discussed.

Kaplan and Katz<sup>23</sup> have described the characteristic electrocardiographic patterns in left ventricular strain with and without axis deviation. Mortensen<sup>24</sup> has contributed an interesting article on bundle-branch block with particular reference to the changes observed in the chest leads. Other interesting articles include Bachmann's<sup>25</sup> report on the significance of splitting of the P waves, Knies's<sup>26</sup> report on the electrocardiogram in induced fever, Larsen and Skulason's<sup>27</sup> studies on the normal electrocardiogram and Levine and Beeson's<sup>28</sup> and Wolferth and Wood's<sup>29</sup> reports on short PR and wide QRS anomaly.

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22. Weinberg, H. B., and Katz, L. N.: A Common Electrocardiographic Variant Following Acute Myocardial Infarction, *Am. Heart J.* **21**:699, 1941.

23. Kaplan, L. G., and Katz, L. N.: The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation, *Am. J. M. Sc.* **201**:676, 1941.

24. Mortensen, V.: Pathogenesis of Bundle Branch Block and Other Preponderance Curves, *Acta med. Scandinav.* **104**:267, 1941.

25. Bachmann, G.: The Significance of Splitting of the P-Wave in the Electrocardiogram, *Ann. Int. Med.* **14**:1702, 1941.

26. Knies, P. T.: The Electrocardiogram in Induced Fever, *Am. Heart J.* **22**:804, 1941.

27. (a) Larsen, K., and Skulason, T.: The Normal Electrocardiogram: I. Analysis of the Extremity Derivations from One Hundred Normal Persons Whose Ages Ranged from Thirty to Fifty Years, *Am. Heart J.* **22**:625, 1941. (b) Skulason, T., and Larsen, K.: The Normal Electrocardiogram: II. Analysis of Precordial Derivations *d* and *s* from One Hundred Normal Persons Whose Ages Ranged from Thirty to Fifty Years, *ibid.* **22**:645, 1941.

28. Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome, with Paroxysms of Ventricular Tachycardia, *Am. Heart J.* **22**:401, 1941.

29. Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association with Prolongation of the QRS Complex, *Am. Heart J.* **22**:450, 1941.

## CARDIAC ARRHYTHMIAS

*Ventricular Fibrillation.*—Wiggers and his associates<sup>30</sup> have reported their further observations on ventricular fibrillation in dogs. They measured the fibrillation thresholds in normal dogs' hearts and during brief coronary occlusion. From this study they describe the probable mechanism which initiates spontaneous ventricular fibrillation following coronary occlusion. Acute ischemia

. . . gives rise to many ectopic foci which release stimuli which are sub-threshold as far as induction of fibrillation in the normal myocardiogram is concerned and it increases irritability sufficiently so that these stimuli become effective when they fall during the vulnerable phase.

*Stokes-Adams Attacks.*—Parkinson, Papp and Evans<sup>31</sup> have discussed the Stokes-Adams attack after a study of cases (8 of their own and 56 collected from the literature) in which an electrocardiogram was recorded during the period of unconsciousness. They would limit the meaning of the term and define it as follows:

Stokes-Adams disease is a name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these.

During a Stokes-Adams attack from ventricular standstill the auricle continues to beat, whereas in other cardiac syncope as a rule there is total cardiac standstill.

The term cardiac syncope may be reserved for attacks in patients without heart block due to total cardiac standstill from neurogenic or myocardial causes.

The authors point out that although it is widely believed that ventricular standstill is the only common disturbance of mechanism which determines loss of consciousness, there are other disturbances of rhythm which may be responsible for the cerebral attack. The following classification is given:

Group I. Ventricular standstill alone (33 of 64 cases). Although this is sometimes consecutive to an increase in ventricular rate, it is unlikely that exercise or emotion is more than a rare precipitating factor; the increase in auricular rate is probably spontaneous and originates in the auricle or the node itself. During a short ventricular standstill (below 20 seconds) the auricle beats regularly, whereas in a long ventricular standstill (above 20 seconds), as when it is preceded by high

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30. (a) Wiggers, C. J.: The Ineffectiveness of Vagal Stimulation on Ventricular Fibrillation in Dogs, *Am. J. Physiol.* **133**:634, 1941. (b) Moe, G. K.; Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of the Fibrillation by Electrocardiographic Studies, *ibid.* **134**:473, 1941. (c) Wegria, R.; Moe, G. K., and Wiggers, C. J.: Comparison of Vulnerable Periods and Fibrillation Thresholds of Normal and Idioventricular Beats, *ibid.* **133**:651, 1941.

31. Parkinson, J.; Papp, C., and Evans, W.: The Electrocardiogram of the Stokes-Adams Attack, *Brit. Heart J.* **3**:171, 1941.



ventricular tachycardia and fibrillation, the auricle may slow, arrhythmia may develop or the auricle may stop. The Stokes-Adams attack due to ventricular standstill and that due to high ventricular tachycardia or ventricular fibrillation can be distinguished only by electrocardiogram. A late onset of consciousness or loss of consciousness of more than three minutes' duration is rarely due to ventricular standstill. The prognosis for patients showing ventricular standstill alone is much better than that for those showing high or low ventricular tachycardia and fibrillation.

Group II. Ventricular tachycardia followed by ventricular standstill.

- (a) Low ventricular tachycardia (rate below 160) followed by ventricular standstill (4 cases). Low ventricular tachycardia does not produce unconsciousness, but it provokes the subsequent ventricular standstill which, of course, does cause unconsciousness.
- (b) High ventricular tachycardia (rate between 200 and 500), usually also with ventricular fibrillation, followed by ventricular standstill (14 cases). The high ventricular tachycardia and fibrillation produce unconsciousness which may be prolonged by the subsequent standstill.

Group III. High ventricular tachycardia or ventricular fibrillation or both without ventricular standstill (13 cases). The prognosis both of the immediate attack and of survival is poor for patients in groups II and III.

Group IV. Extreme bradycardia with complete heart block. This is a small and unimportant group.

*Auricular Fibrillation.*—Modell, Gold and Rothendler<sup>32</sup> have shown that in the average patient with auricular fibrillation the increase in rate during exercise is due chiefly to decrease in vagal tone. Some confirmation of this fact was found in the observation that the increase in heart rate following atropinization was similar to the increase in rate after severe exercise. If patients with auricular fibrillation are given relatively large doses of digitalis ("extravagal" digitalization), the exaggerated acceleration of the ventricles caused by exercise can usually be prevented. They conclude that the small increase in rate following administration of large amounts of digitalis is due to the direct action of this drug on auriculoventricular conduction.

*Hubbard's Syndrome.*—Hubbard<sup>33</sup> has described a newly observed clinical syndrome, the course of which is circulatory failure resulting from paroxysmal tachycardia in infants less than 12 months of age. The incidence is unknown, but it is of interest that the author observed

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32. Modell, W.; Gold, H., and Rothendler, H. H.: Use of Digitalis to Prevent Exaggerated Acceleration of the Heart, *J. A. M. A.* **116**:2241 (May 17) 1941.

33. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, *Am. J. Dis. Child.* **61**:687 (April) 1941.

6 of his 9 cases within a year, yet was able to collect only 19 cases from the medical literature. The diagnosis may be made clinically, but because of the difficulty in counting the pulse or even the heart rate accurately in young infants, electrocardiograms should always be obtained. The signs and symptoms are characteristic and include vomiting, which may be severe; dyspnea, with a respiratory rate as high as 160 per minute; fever; leukocytosis, and marked congestive phenomena, including cyanosis, cardiac enlargement, pulmonary congestion, engorgement of the liver and edema of dependent parts. The prognosis is unfavorable unless digitalis is promptly given. The recommended initial dose is 0.05-0.1 Gm. of digifoline intramuscularly, and this should be repeated at intervals (once or twice a day) until the desired effect is obtained. After digitalization has been accomplished, the heart rate and rhythm return to normal, and clinical improvement follows with dramatic abruptness. This condition has as a rule been wrongly diagnosed, for example, as congenital idiopathic hypertrophy, pyloric stenosis and pneumonia. The prognosis is apparently good, and there is little tendency for the arrhythmia to recur.

*Potassium.*—Despite the extensive knowledge of potassium metabolism and the part it plays in heart muscle contraction, there is some doubt and confusion with reference to the therapeutic use of potassium salts in cardiac arrhythmias. For many years the use of potassium was recommended for abolishing or preventing premature beats and paroxysmal tachycardia, and there is no doubt that this was attended with some success. On the other hand, it has also been pointed out by several observers that certain types of cardiac arrhythmia and alterations in the electrocardiogram result from the administration of potassium salts.

A partial explanation of these apparently conflicting results has been offered by Castleden,<sup>34</sup> and it would appear that in some patients, at least, with abnormally low serum potassium levels cardiac arrhythmias and electrocardiographic abnormalities can be abolished by administering potassium salts, whereas in patients with normal serum potassium levels who are given potassium salts cardiac irregularities and electrocardiographic abnormalities may develop.

#### CONGENITAL HEART DISEASE

Bedford, Papp and Parkinson<sup>35</sup> have reported at length their observations on atrial septal defect. They point out that this is one of the commonest congenital malformations and should be differentiated

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34. Castleden, L. I. M.: The Effect of Potassium Salts on Cardiac Irregularities, *Brit. M. J.* **1**:7, 1941.

35. Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, *Brit. Heart J.* **3**:37, 1941.

from patent foramen ovale, which is simply an anatomic variation of a normal condition. The diagnosis of atrial septal defect can often be made clinically. Although this defect itself produces no murmurs, the accompanying dilatation of the right ventricle and conus and relative stenosis of the less distensible pulmonary ring account for the loud systolic murmur heard over the pulmonary area in three fifths of the cases. Accentuation of the pulmonary second sound is likewise a common finding, and an accompanying thrill is sometimes felt and a pulmonary diastolic murmur sometimes heard. The roentgen features are characteristic and include general enlargement of the heart, bulging of the pulmonary stem and conus and a dense shadow in the right hilus, with excessive pulsation. The electrocardiogram is often helpful in diagnosis, particularly the presence of right axis deviation. The association of mitral stenosis and atrial septal defect is stressed.

#### RHEUMATIC HEART DISEASE

*Etiology.*—Mote and Jones<sup>36</sup> have reported their extensive observations on the antibody responses to hemolytic streptococci in patients with primary or recurrent rheumatic fever. The antibody response was also studied in healthy persons and in patients with scarlet fever and with acute streptococcic pharyngitis. It was found that the rheumatic and the nonrheumatic patients have similar antibody responses to acute infection with hemolytic streptococci. Also, severe rheumatic infection may develop in patients without clinical or serologic evidence of infection with streptococci, or, on the other hand, streptococcic infection may occur in a rheumatic subject without precipitating active rheumatic fever. Mote and Jones's contribution is important but still leaves unexplained the exact role played by streptococci in the causation of rheumatic fever.

Kuttner and Krumwiede<sup>37</sup> have described in some detail the effects of three outbreaks of streptococcic infection of the upper respiratory

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36. (a) Mote, J. R., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: I. The Incidence of Antistreptolysin 'O', Antifibrinolysin, and Hemolytic Streptococcal Precipitating Antibodies in the Sera of Urban Control Groups, *J. Immunol.* **41**:35, 1941; (b) Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: II. The Frequency of Antistreptolysin 'O', Antifibrinolysin, and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, *ibid.* **41**:61, 1941; (c) Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: III. The Magnitude of Antistreptolysin 'O', Antifibrinolysin, and Precipitating-Antibody Responses; the Persistence of the Antibodies, and Variations in Antistreptolysin 'O' Curves in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, *ibid.* **41**:87, 1941.

37. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study, *J. Clin. Investigation* **20**:273, 1941.

tract in a colony of rheumatic children. The incidence of rheumatic recurrences was found to vary greatly, but a comparison of the epidemic strains of streptococci and of the clinical features of the infections failed to reveal any significant differences to account for this. The authors conclude that the vulnerability of a rheumatic subject to the effects of streptococcic infection of the upper respiratory tract is variable and depends on factors not yet understood.

Reyersbach, Lenert and Kuttner<sup>38</sup> studied an outbreak of influenza due to influenza virus B in a group of rheumatic children. No rheumatic recurrences were precipitated, and no evidence was obtained to suggest that the virulence of a group A beta hemolytic *Streptococcus* of proved pathogenicity was increased by this strain of influenza virus.

Glazebrook and Thomson<sup>39</sup> have briefly reported 11 instances of rheumatic fever in which the first evidence of rheumatic arthritis was in a traumatized joint. Their data do not prove that trauma was the sole, or even the chief, precipitating factor in the rheumatic infection, but there is little doubt that the trauma determined the initial location of joint disease.

*Rheumatic Pneumonia.*—Epstein and Greenspan<sup>40</sup> have reported their observations on the pulmonary changes in 45 cases of acute fatal rheumatic fever. They found characteristic pulmonary changes, including alveolitis, marked congestion, edema, engorgement and the formation of hyaline membranes but do not consider these changes specific; i. e., a specific rheumatic lung or rheumatic pneumonia cannot be considered to exist.

*The Pulse Rate in Acute Rheumatism.*—Glazebrook and Thomson<sup>41</sup> observed the pulse rate in 100 consecutive cases of acute rheumatism in boys and youths aged 15 to 20 years. They found that slowing of the pulse rate is a common feature in the initial stages of the first attack of rheumatic infection but that all patients showed tachycardia in the later stages. They divided the 100 cases into three groups. In the 38 cases in the first group the pulse rate was commensurate with the body temperature. There was some increase in pulse rate in the second group of 32 cases, but this increase was not commensurate with the temper-

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38. Reyersbach, G.; Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations, *J. Clin. Investigation* **20**:289, 1941.

39. Glazebrook, A. J., and Thomson, S.: Acute Rheumatism and Trauma, *Edinburgh M. J.* **48**:674, 1941.

40. Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia, *Arch. Int. Med.* **68**:1074 (Dec.) 1941.

41. Glazebrook, A. J., and Thomson, S.: The Pulse Rate in Acute Juvenile Rheumatism, *Edinburgh M. J.* **48**:619, 1941.

ature. Bradycardia occurred at an early stage of the illness in the remaining 30 cases which composed the third group and was usually a transient phenomenon. Bradycardia was sometimes associated with marked sinus arrhythmia and prolongation of the PR interval, all of which may have been due to vagal overstimulation. It was found that an abnormally slow pulse rate in the early stages of the rheumatic infection is of grave prognostic significance insofar as permanent cardiac damage is concerned.

*Electrocardiographic Changes.*—Orgain, Martin and Anderson<sup>42</sup> have reviewed previous studies on the electrocardiographic alterations in rheumatic fever in children and reported their own observations on 70 patients. Abnormalities in single or serial tracings were found in 70 per cent of the 70 patients. They found that the electrocardiograms were abnormal in all of the 22 patients who had the most extensive myocardial damage.

*Complications.*—Harris and Levine<sup>43</sup> studied 72 cases of mitral stenosis in which cerebral embolism occurred. There were 24 "immediate fatalities," and in the 15 cases in which the patients died subsequently the average period of survival was a little over one year. Auricular fibrillation was present in 55 cases and regular rhythm in the remaining 17. In 5 instances cerebral embolism occurred a few hours or a day or two after a change from auricular fibrillation to normal rhythm. The difficulties of analyzing the factors responsible for the formation and dislodgment of auricular thrombi are emphasized. Despite the general assumption that auricular fibrillation increases the likelihood of thrombosis and embolism, Harris and Levine on the basis of their studies could not prove this assumption.

Wolff and Levine<sup>44</sup> found that about 10 per cent (50 of 521) of their series of patients with rheumatic heart disease had had hemoptysis. Mitral stenosis was present in every patient save 1 in which the hemorrhage was caused by a pulmonary abscess. The hemorrhage was accounted for by pulmonary infarction in almost half of the patients, but if the heart is not enlarged it can be excluded as a cause. Hemorrhage may be caused by active rheumatic infection or by mitral stenosis alone. The three most commonly associated symptoms were palpitation, pain in the chest and dyspnea. Insofar as prognosis is concerned hemoptysis is a grave sign.

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42. Orgain, E. S.; Martin, J. M., and Anderson, H. I. G.: Electrocardiographic Alterations in Rheumatic Fever in Children, *Am. J. Dis. Child.* **62**:26 (July) 1941.

43. Harris, A. W., and Levine, S. A.: Cerebral Embolism in Mitral Stenosis, *Ann. Int. Med.* **15**:637, 1941.

44. Wolff, L., and Levine, H. B.: Hemoptysis in Rheumatic Heart Disease, *Am. Heart J.* **21**:163, 1941.

*Treatment.*—Early studies on the use of sulfanilamide and some of its derivatives in the treatment of rheumatic heart disease, which have been previously reviewed,<sup>45</sup> led to the conclusion that during the active stage of the disease toxic rather than beneficial results were obtained, but that the long-continued prophylactic use of sulfanilamide prevented hemolytic streptococcic infection and recurrences of rheumatic fever. A further report by Thomas, France and Reichsman<sup>46</sup> has confirmed the earlier impression regarding the prophylactic use of sulfanilamide. The results of their carefully controlled studies are striking. A major attack of acute rheumatic fever or an acute infection caused by beta hemolytic streptococci did not develop in any of the 55 patients (79 person-seasons) who received sulfanilamide (usually 0.6 Gm. twice a day from November through June). Fifteen major attacks of acute rheumatic fever occurred in 67 patients (150 person-seasons) with a similar history who did not receive the drug. Furthermore, 4 deaths occurred in the control (nontreated) group, 2 as a result of subacute bacterial endocarditis, whereas there were no deaths among patients in the treated group. No serious toxic effects of sulfanilamide were observed. Thus, the studies of Thomas and associates, as well as those of others, point the way toward a better treatment of patients susceptible to rheumatic fever. These studies also add further proof of the close relation between infections caused by beta hemolytic streptococci and rheumatic infection.

#### SUBACUTE BACTERIAL ENDOCARDITIS

Although the results of chemotherapy of subacute bacterial endocarditis<sup>47</sup> have been disappointing, it is better than anything previously

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45. (a) Graybiel, A.: Diseases of the Heart: A Review of Significant Contributions Made During 1938, *Arch. Int. Med.* **63**:980 (May) 1939. (b) Graybiel and White.<sup>14</sup>

46. Thomas, C. B.; France, R., and Reichsman, F.: The Prophylactic Use of Sulfanilamide, *J. A. M. A.* **116**:551 (Feb. 15) 1941.

47. (a) Leach, C. E.; Faulkner, J. M.; Duncan, C. N.; McGinn, S.; Porter, R. R., and White, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis, *J. A. M. A.* **117**:1345 (Oct. 18) 1941. (b) Druckman, J. S.: A Case of Subacute Bacterial Endocarditis, *ibid.* **117**:101 (July 12) 1941. (c) Heyer, H. E., and Hick, F. K.: Experiences in the Treatment of Subacute Bacterial Endocarditis with Sulfanilamide, Sulfapyridine and Sulfathiazole: A Review of Previously Reported Cured Cases with the Report of Fifteen Treated Cases Including One Cure and One Aborted Case, *Ann. Int. Med.* **15**:291, 1941. (d) Kinsella, R. A.: Chemotherapy of Bacterial Endocarditis Caused by a Hitherto Undescribed Gram Negative Coccus, *ibid.* **15**:756, 1941. (e) Weber, F. P.: Recovery from the Infection of Subacute Bacterial Endocarditis Without Sulphonamides, *Lancet* **1**:630, 1941. (f) Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhopara-

tried. Probably cure is obtained in 1 case in 20 today, whereas spontaneous cures in the past were exceedingly rare indeed. Heparin, hyperpyrexia and fever induced by injection of typhoid vaccine have been used in conjunction with sulfanilamide and some of its derivatives, but enthusiasm for any combination treatment is waning. Sulfapyridine, (2-[paraaminobenzenesulfonamido]-pyridine), of the various compounds, seems to be the best, and it is advisable to keep the level of the drug in the blood high (10 mg. per hundred cubic centimeters) for at least a month, then to continue administering a reduced dose for two or three months longer. If the results are not promising, a change to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) should be made.

The most promising results are being obtained in patients with patent ductus arteriosus complicated by subacute bacterial endoarteritis.<sup>48</sup> Obliteration of the ductus by surgical means together with chemotherapy has now resulted in a number of cures.

#### OTHER INFECTIONS

*Scarlet Fever.*—Wesselhoeft<sup>49</sup> has had the unusual experience of studying over 12,000 cases of scarlet fever and must be regarded as an authority on the cardiovascular disorders or complications in this disease. He points out that the endocarditis which may develop in the course of scarlet fever is the result of infection of the blood stream and constitutes a true bacterial endocarditis. He does not believe that scarlet fever causes valvular endocarditis comparable to that seen in rheumatic infection; a valvular defect which appears late after scarlet fever should be considered to be of rheumatic origin. Severe myocarditis, such as may occur in the course of diphtheria, is rarely observed in scarlet fever, and when it occurs, there is a strong possibility that diphtheria is present as a complication. Wesselhoeft states that of 9 cases of severe myocarditis among 12,820 cases of scarlet fever, cultures positive for the diphtheria bacillus were obtained in 6. He discusses in some detail

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typhoid Vaccine, New York State J. Med. **41**:45, 1941. (g) Southworth, H.: Subacute Staphylococcus Endocarditis and Staphylococcus Bacteremia Without Endocarditis with a Report of the Favorable Effect of Sulfanilamide and Sulfathiazole in Two Cases, Ann. Int. Med. **14**:1180, 1941. (h) Sevitt, S.: Treatment of Bacterial Endocarditis with Heparin and Sulfapyridine, Lancet **1**:444, 1941. (i) McLean, J.; Meyer, B. B. M., and Griffith, M. F.: Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1870 (Nov. 29) 1941. (j) Cockayne, E. A., and Wilton, T. N. P.: Acute Bacterial Endocarditis, Lancet **2**:728, 1941.

48. Bourne, G.; Keele, K. D.; Tubbs, O. S., and Swain, R. H. A.: Ligation and Chemotherapy for Infection of Patent Ductus Arteriosus, Lancet **2**:444, 1941.

49. Wesselhoeft, C.: Cardiovascular Disorders in Scarlet Fever, New England J. Med. **224**:22, 1941.

the so-called "scarlet fever heart," diagnosis of which is usually dependent on the development of murmurs which are so variable in time and character as not to be distinctive. Tachycardia or bradycardia may develop, but there is rarely any cardiac enlargement, and there is no precordial pain or discomfort. All these signs are ephemeral and disappear in the course of one to three weeks.

Wesselhoef agrees that minor electrocardiographic abnormalities may appear, but states that they are not peculiar to scarlet fever and do not constitute proof of myocarditis. Roelsen,<sup>50</sup> however, believes that the more significant and persistent electrocardiographic changes are probably due to pathologic changes in the myocardium, but that the slight and transient changes are likely due to myocardial toxemia.

With respect to treatment Wesselhoef believes that in the toxic myocarditis accompanying scarlet fever specific drugs are of no value, but that if endocarditis or pericarditis of bacterial origin supervene, sulfanilamide should be given.

*Tuberculosis.*—Hannesson<sup>51</sup> has written an excellent article on tuberculosis of the pericardium and the heart. He states that although the myocardium and the endocardium are rarely involved in tuberculosis, involvement of the pericardium is not as rare as is generally supposed and is the most serious tuberculous infection of the serous membranes. He believes that most instances of tuberculous pericarditis are due to an extension of the infection through lymph channels from a mediastinal focus, but that infection may occur in a neighboring structure. Hannesson divides the pathologic progress in a typical case into three stages. An acute fibrinous stage passes fairly rapidly into the stage of pericardial thickening and effusion. The third stage is that in which the effusion has largely disappeared and the pericardium is greatly thickened. This may be so extensive as to give rise to typical Pick's disease.

The author points out that tuberculous pericarditis is protean in its clinical manifestations and that the clinical features depend on the nature of the onset, the type of pathologic changes, the duration of the disease and other factors. The symptomatology and clinical features are described in detail. He summarizes the important findings necessary to make a diagnosis of tuberculous pericarditis as follows:

The signs and symptoms of an infection should be present; there should be localizing signs over the pericardium such as pericardial friction rub, signs of pericardial effusion and thickening of the pericardium, and the signs of adhesions. There should be signs of circulatory failure of the "inflow stasis" type; there should be signs of extension of the process to other serous sacs or a disseminated

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50. Roelsen, E.: Electrocardiographic Studies in Scarlet Fever, *Acta med. Scandinav.* **106**:1, 1941.

51. Hannesson, H.: Tuberculosis of the Pericardium and Heart, *Tubercle* **22**: 79, 1941.



tuberculosis; a normal or small heart should be demonstrated after the production of a pneumopericardium; a careful x-ray study should be made.

A clinical diagnosis can be made on the results of a careful physical and radiological examination.

An exact diagnosis can only be made by demonstration of tubercle bacilli in the pericardial fluid.

Hannesson points out that present methods of treatment of tuberculous pericarditis are unsatisfactory and that the prognosis is bad (83 per cent). It is of interest that he considers polyserositis in all probability to be tuberculous in origin and a condition associated with a high degree of immunity to the infection. He was unable to determine any exact relation between pulmonary tuberculosis and diseases of the heart.

#### ARTERIAL HYPERTENSION

*Experimental Aspects.*—Because of the importance of this subject, it seems worthwhile to review again the main developments and the present status of knowledge with regard to experimental hypertension and the resulting clinical implications. The current phase of this work began with the demonstration by Goldblatt that if one or both of the main renal arteries of a dog were partially occluded by a metal clamp, hypertension would result.

This was quickly confirmed by many other investigators and amplified to the extent that various methods were shown to be capable of producing lasting hypertension ranging from the benign to the malignant variety.

An immediate search was begun for the factors or substances responsible for the hypertension, and largely by the process of exclusion, it was soon shown that a humoral factor elaborated by the kidney was the probable cause. At this point it was recalled that Tigerstedt and Bergmann in 1898 obtained a pressor substance from renal tissue extract, which was called renin, and this seemed the most likely substance to investigate.

The characteristics of renin have been studied extensively, and it has been shown that a renin-like substance is liberated in increased amounts by the kidneys of dogs made hypertensive by one of the several available methods. However, attempts to demonstrate an increased amount of renin in the extracts of kidneys of hypertensive patients as compared with normal controls has not yet yielded convincing results.<sup>52</sup>

Page and his associates have shown that purified renin alone does not cause vasoconstriction when perfused in Ringer's solution through a rabbit's ear. It requires the addition of a substance found normally in plasma which has been given the name "renin-activator." The product

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52. Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys, *Am. J. M. Sc.* 202:14, 1941.

of the interaction between renin and renin-activator is a third substance, to which Page has given the name angiotonin.

Angiotonin exerts a powerful vasopressor action<sup>53</sup> but is distinguishable from most other pressor substances in that it does not appreciably diminish cutaneous blood flow. Much more important is the fact that animals which have received repeated injections of renin fail to respond with a rise in arterial pressure (tachyphylaxis), which appears to be due to the release of a substance which antagonizes renin or its reaction product angiotonin. Studies along this line<sup>54</sup> have definitely shown that this substance which opposes the action of angiotonin is elaborated in the kidneys and is capable of lowering the blood pressure. Grollman and his associates, Page and his co-workers and the Argentinian investigators have obtained this antipressor substance, using different methods. All groups of workers have had some success in lowering the blood pressure in animals made hypertensive and in patients with essential or malignant hypertension. Page and his associates have now administered this extract to 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with essential hypertension. They found that the extract prepared from 400 to 900 Gm. of fresh pork kidney is usually required to reduce the blood pressure of a dog weighing 12 Kg. from 200 to 130 mm. of mercury. The extracts were usually given in moderate doses daily. Arterial pressure began to fall in two to four days, reaching nearly normal levels in five to eight days. Discontinuing the extract did not lead to an immediate rise in blood pressure; usually several days elapsed before there began a gradual rise in pressure to the original hypertensive level. Good results were also obtained in dogs

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53. Page, I. H.: The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin, *Am. J. Physiol.* **134**:789, 1941.

54. (a) Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, *Proc. Soc. Exper. Biol. & Med.* **46**:244, 1941. (b) Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man, *J. Clin. Investigation* **20**:715, 1941. (c) Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, *ibid.* **20**:721, 1941. (d) Grollman, A.; Williams, J. R., Jr., and Harrison, T. R.: The Reduction of Elevated Blood Pressure by Administration of Renal Extracts, *J. A. M. A.* **115**:1169 (Oct. 5) 1940. (e) Jensen, H.; Corwin, W. C.; Tolksdorf, S.; Casey, J. J., and Bamman, F.: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts, *J. Pharmacol. & Exper. Therap.* **73**:38, 1941. (f) Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Kempf, G. F.; Gambill, W. D., and Taylor, R. D.: The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals, *Ann. Int. Med.* **15**:347, 1941. (g) Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Fouts, P. J., and Kempf, G. F.: Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals with Extracts of Kidneys, *J. Exper. Med.* **73**:7, 1941.

made severely hypertensive and exhibiting the malignant syndrome. The blood urea nitrogen usually falls as the blood pressure drops, and there may be dramatic clinical improvement.

After one reads the 19 case histories reported by Page and associates the general impression is gained that the treatment of severe hypertension by means of renal extracts is still far from satisfactory. Systolic and diastolic blood pressures are lowered significantly in some cases, and associated with this there is considerable clinical improvement. However, severe reactions are often encountered, with symptoms resembling shock and followed by fever. These untoward side-effects prohibit this form of treatment in cases of mild essential hypertension in which the best results would be expected. There is, as yet, no sure proof that these extracts have more than a nonspecific effect, but with further purification this important point should be clarified. The many investigators in various centers working on this problem should be encouraged to continue. Their work represents a hopeful line of research in the pathogenesis and treatment of hypertension.

Bing and Zucker<sup>55</sup> have studied the pressor effect of several amino acids metabolized by the ischemic kidney. It is known that certain renal extracts transform amino acids into the corresponding amines, some of which have a pressor action. Normally, these amines are broken down into physiologically inert end-products, but under anaerobic conditions this is prevented and the amines are free to exert their pressor action. The authors put this to a practical test by injecting amino acids into the kidneys of experimental animals. With the renal circulation intact no significant pressor effects were noted, but when the circulation was restricted the arterial pressure rose. That altered amino acid metabolism may be responsible for renal hypertension is the interesting suggestion put forth.

Wilson and Byrom<sup>56</sup> have contributed important experimental observations which go a long way toward explaining the clinical and histologic manifestations which are common to the end stages of Bright's disease. They produced hypertension in rats by partial occlusion of one renal artery. After a time the clamped kidney was removed, but residual hypertension remained in two thirds of the animals. The degree of hypertension was found to be related to the extent of the lesions in the remain-

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55. (a) Bing, R. J.: The Formation of Hydroxytyramine by Extracts of Renal Cortex and by Perfused Kidneys, *Am. J. Physiol.* **132**:497, 1941. (b) Bing, R. J., and Zucker, M. B.: The Formation of Pressor Amines in the Kidney, *Proc. Soc. Exper. Biol. & Med.* **46**:343, 1941; (c) Renal Hypertension Produced by Amino Acids, *J. Exper. Med.* **74**:235, 1941.

56. Wilson, C., and Byrom, F. B.: The Vicious Circle in Chronic Bright's Disease: Experimental Evidence from the Hypertensive Rat, *Quart. J. Med.* **10**: 65, 1941.

ing kidney, which resemble those occurring in cases of chronic hypertensive Bright's disease. They conclude that their findings support the concept of a vicious circle resulting from the effect of hypertension on the kidney whereby hypertension produces vascular lesions and these, by reducing the blood flow through the kidney, aggravate the hypertension, which in turn leads to sustained hypertension and progressive renal destruction.

#### CORONARY ARTERIOSCLEROTIC HEART DISEASE

*Etiology.*—From a long experience Hueper<sup>57</sup> has formulated a definite opinion regarding the etiology and the causative mechanism of arteriosclerosis and atheromatosis. His introduction is as follows:

No agreement has been reached concerning the respective roles played in the production of these lesions, on the one hand by physiological senescing processes, possibly conditioned in their time of onset, in their rate of progress, and in their organic distribution by constitutional or hereditary factors, and on the other hand by pathological disturbances of endogenous or exogenous origin and of acquired nature. The situation existing in this respect is complicated by the fact that these vascular manifestations exhibit a remarkable diversity in their anatomical structure, as evidenced by the various names used, such as arteriosclerosis, atheromatosis, atherosclerosis, Monckeberg's media necrosis and calcification, etc., indicating that several fundamentally different causal factors may be reflected by these morphological varieties. The same conclusion is suggested by the observation that there occurs a considerable disparity in the organic distribution and in the time of appearance of these lesions in the different organs. None of the numerous theories so far advanced concerning the etiology of degenerative vascular disease supplies a satisfactory explanation of the multitude and variety of phenomena, or provides an acceptable common denominator of the primary causal dynamics operating in their production.

Hueper then discusses a number of endogenous and exogenous factors of a physical and chemical nature which have been considered etiologically significant in the development of vascular lesions. These are grouped under five headings, namely, (1) physiologic senescing processes, (2) physiologic and pathologic mechanical traumas, (3) infections and bacteriotoxic agents, (4) physiochemical disturbances of the blood of endocrine, vitaminic or nutritive origin and (5) agents affecting the vascular tonus and the circulation of the blood. He reaches the general conclusion that the fundamental causal mechanism of degenerative arterial disease is impaired nutrition and oxygenation of the vascular wall, resulting in endothelial damage, increased intimal permeability and the infiltration of plasma into the subintimal tissue followed by the proliferation of endothelial cells and the degeneration of the muscular and the elastic cells.

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57. Hueper, W. C.: The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis, *Medicine* 20:397, 1941.

Hueper emphasizes that a rational therapeutic management of arteriosclerotic patients depends in part on the determination of the etiologic agent, which is admittedly difficult because of the great complexity of present day life. But, says Hueper, the outstanding therapeutic procedure, apparently capable of preventing the development of or arresting the progress of arteriosclerosis of varying causation, is represented by a maintenance of an adequate oxygen metabolism; thyroid and iodine preparations have proved so far to be the most suitable agents for attaining this end, particularly in cases in which an endogenous disturbance of the oxygen metabolism prevails.

*The Precipitating Factors in Coronary Occlusion.*—Paterson<sup>58</sup> has again emphasized the important role of intimal hemorrhage in producing coronary thrombosis. This hypothesis has received strong support from various investigators and most recently from Nelson.<sup>59</sup> He observed that hemorrhage from sinusoidal blood vessels which are found in relation to atheromatous plaques is not uncommon and that superficial intimal hemorrhage is a most important factor in the causation of coronary occlusion. Nelson is in agreement with Paterson that the factors determining the hemorrhage are probably weakening of the sinusoidal wall by toxic action and increase in blood pressure induced by exertion or emotion. Paterson<sup>58</sup> considers that increased capillary fragility due to vitamin C deficiency may also be a causative factor and that calcification of atherosclerotic plaques may be a protection against intimal hemorrhage and recommends an ample calcium intake.

Blumgart, Schlesinger and Zoll<sup>60</sup> in a study of the clinical and pathologic findings in a series of 350 cases observed multiple fresh coronary occlusions in 11. In 8 of the 11 cases multiple fresh thrombi had occluded the arteries, while in the remaining 3 the multiple occlusions were due to hemorrhages within atheromatous plaques and to ruptured atheromatous abscesses. In each instance the multiple occlusions occurred in the presence of shock which was due to conditions other than myocardial infarction in 8 of the 11 cases. They conclude that shock, no matter how produced, may lead in elderly patients to the development not only of single but of multiple fresh coronary artery occlusions and that measures to prevent the manifestations of shock should always be taken.

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58. Paterson, J. C.: Some Factors in Causation of Intimal Hemorrhages and in Precipitation of Coronary Thrombi, *Canad. M. A. J.* **44**:114, 1941.

59. Nelson, M. G.: Intimal Coronary Artery Hemorrhage as a Factor in the Causation of Coronary Occlusion, *J. Path. & Bact.* **53**:105, 1941.

60. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, *Arch. Int. Med.* **68**:181 (Aug.) 1941.

*Clinical Aspects.*—Walsh and his associates<sup>61</sup> found that disease of the gallbladder occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries, probably primarily because of some common aging factor and not more intimate connection, whereas there was no significant association of peptic ulcer and coronary disease in general. Hochrein and Schleicher,<sup>62</sup> on the other hand, believe that there is a close relation between coronary insufficiency and peptic ulcer and cite clinical observations to this effect. Rosenbaum and Levine<sup>63</sup> have studied various clinical and electrocardiographic features of acute myocardial infarction and conclude that although the immediate outlook is difficult to predict and the ultimate course varies a great deal, a careful weighing of all the available information will materially aid in judging the prognosis. Bland and White<sup>64</sup> have obtained the after-history for the first ten years of 200 patients with coronary occlusion and acute myocardial infarction; of the entire series, 19 per cent died within the first four weeks and 31 per cent of the remainder survived the ten year period. Master, Dack and Jaffe<sup>65</sup> have summarized their studies which have been in part previously reviewed, based on the analysis of 1,700 proved attacks, especially on precipitating factors in coronary occlusion and myocardial infarction. Stroud and Wagner<sup>66</sup> have reported their findings in 49 cases of proved myocardial infarction in 13 of which the patients were without pain; they discuss various pain "equivalents" and emphasize the importance of recognizing painless infarction.

*Induced Anoxemia in Patients with Coronary Arteriosclerotic Heart Disease.*—Levy and his associates<sup>67</sup> have reported further on the

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61. Walsh, B. J.; Bland, E. F.; Taquini, A. C., and White, P. D.: Association of Gallbladder Disease and of Peptic Ulcer with Coronary Disease: Postmortem Study, *Am. Heart J.* **21**:689, 1941.

62. Hochrein, M., and Schleicher, I.: Peptic Ulcer and Angina Pectoris, *München. med. Wchnschr.* **88**:328, 1941.

63. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction, *Arch. Int. Med.* **68**:912 (Nov.) 1941.

64. Bland, E. G., and White, P. D.: Coronary Thrombosis (with Myocardial Infarction) Ten Years Later, *J. A. M. A.* **117**:1171 (Oct. 4) 1941.

65. Master, A. M.; Dack, S., and Jaffe, H. L.: (a) Premonitory Symptoms of Acute Coronary Occlusion: Study of Two Hundred and Sixty Cases, *Ann. Int. Med.* **14**:1155, 1941; (b) Role of Effort, Work and Occupation on Onset and Subsequent Course of Coronary Artery Occlusion, *M. Ann. District of Columbia* **10**:79, 1941.

66. Stroud, W. D., and Wagner, J. A.: Silent or Atypical Coronary Occlusion, *Ann. Int. Med.* **15**:25, 1941.

67. Levy, R. L.; Williams, N. E.; Bruenn, H. C., and Carr, H. A.: The "Anoxemia" Test in the Diagnosis of Coronary Insufficiency, *Am. Heart J.* **21**:634, 1941.

"anoxemia test" in the diagnosis of coronary insufficiency. The test consists of having the patient breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or until symptoms appear; electrocardiograms are taken before, during and after the induction of anoxemia. This test was performed on 115 normal persons and 147 patients with suspected or manifest cardiac disease. On the basis of this experience the response to the test was considered abnormal when any one (or more) of the following changes was observed:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III and IVF) totals 3 mm. or more.
2. There is partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.
3. There is complete reversal of the direction of T in Lead IVF, regardless of RS-T deviation.
4. There is partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

Levy and co-workers state:

The test was positive in 18 per cent of 33 patients with suspected coronary sclerosis; in 31 per cent of twenty-two patients with coronary sclerosis but no history of anginal attacks; in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks; and in only 5 per cent (one case) of nineteen patients with hypertension without symptoms or signs of coronary sclerosis. Patients whose control electrocardiogram was abnormal showed a higher percentage of positive tests than those with a normal control tracing. The highest incidence of positive tests was obtained in a group of forty-nine patients with anginal pain caused by coronary sclerosis and abnormal control electrocardiograms; in 69 per cent of these an abnormal response was obtained.

Pulmonary edema occurred during the test in 3 instances but was subsequently avoided by observing three rules, namely:

1. The test should never be performed in the presence of congestive heart failure.
2. It should not be performed within 4 months after cardiac infarction.
3. It should not be done on the same patient more than once in twenty-four hours.

Unpleasant effects occurred in 17 cases, including vasovagal attacks, convulsions, hyperventilation, dyspnea and mental confusion, but they did not prove serious.

The authors conclude that a positive test is a sign of functional insufficiency of the coronary circulation and that it may be usefully employed clinically. Williams and associates<sup>68</sup> used this test in evaluating the effects of certain xanthine drugs in cases of coronary insufficiency and concluded that in some cases the therapeutic response is favorable.

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68. Williams, N. E.; Carr, H. A.; Bruenn, H. G., and Levy, R. L.: Further Observations on Effects of Certain Xanthine Compounds in Cases of Coronary Insufficiency, as Indicated by Response to Induced Anoxemia, *Am. Heart J.* **22**:252, 1941.

## MISCELLANEOUS

*Aneurysm of the Pulmonary Artery.*—Boyd and McGavack<sup>69</sup> have presented the clinical picture of aneurysm of the pulmonary artery as a result of a study of 151 recorded instances of this disease. The chief etiologic and precipitating factors were congenital anomalies, pulmonary hypertension, atheromatosis and infection, of which syphilis appeared to have been present and active in over 30 per cent. The authors have divided the cases of pulmonary aneurysm into two main groups, namely, (1) those in which the trunk alone or in combination is involved and (2) those in which one or both branches are affected. They state that the former group is recognizable on the basis of signs and symptoms, whereas in the latter the condition gives rise to symptoms alone. They further state:

Antemortem diagnosis is difficult in both clinical types, but can be established with a fair degree of accuracy in the first group if the following are simultaneously present: stasis in the lesser circulation, characterized by dyspnea, cyanosis, oppression of the chest, and bloody sputum; prominence of the left side of the chest in the region of the second and third costal cartilages; a pulsation, a thrill, and a loud superficial, sawing or rubbing systolic murmur, best heard at the second left intercostal space; a weak cardiac thrust with dulness not going beyond the mid-clavicular line; hypertrophy and dilatation of the right side of the heart; electrocardiographic evidence of right axis deviation; roentgenographic demonstration of lengthening and lateral projection of the pulmonary conus shadow in the anterior view, with a see-saw movement of the left border; indentation of the esophagus below the normal aortic impression in the right anterior oblique position; and encroachment upon the ventral and caudad aspects of the aortic window in the left anterior oblique visualization.

The subjective symptoms are similar in the two groups. Cough occurs in 80 per cent of the cases, but is rarely an early manifestation. It depends upon pressure on the recurrent laryngeal nerve, in which event it is non-productive; upon bronchial irritation with at first a dry, and later a productive phase; or upon pulmonary thromboses when it is blood-streaked or frankly hemorrhagic.

The authors recognize that a number of conditions may simulate the clinical picture of aneurysm of the pulmonary artery and discuss the differential diagnosis. The chief lesions with which it may be confused are aortic aneurysm, patent ductus arteriosus, idiopathic dilatation of the pulmonary artery, interauricular septal defects and other congenital cardiac lesions.

We wish to point out that a clinical diagnosis of uncomplicated pulmonary aneurysm must be regarded with great skepticism, and therefore in 35 of the 151 cases (in which the condition was not confirmed by autopsy) the diagnosis is open to question.

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69. Boyd, L. J., and McGavack, T. H.: Aneurysm of the Trunk and Main Branches of the Pulmonary Artery: Analysis of One Hundred and Fifty-Two Cases, *Mod. Concepts Cardiovasc. Dis.* 10:2, 1941.



*Disseminated Lupus Erythematosus.*—There are a number of disease syndromes, including disseminated lupus erythematosus, dermatomyositis and periarteritis nodosa, the causes of which are unknown but which have certain clinicopathologic features in common, including involvement of the cardiovascular system. The amount of attention they have received from cardiologists is probably greater than is deserved, as there is little evidence that the cardiac changes are more than incidental. Two recent reviews <sup>70</sup> have brought present knowledge up to date, without, however, resolving the problem. The nearest thing to a definite cardiac syndrome appears in those cases of disseminated lupus in which there is atypical verrucous endocarditis (Libman-Sacks syndrome). Despite the characteristic pathologic changes in these lesions, they are, with probable rare exceptions, too slight to yield definite clinical signs of heart disease and are rarely, if ever, the cause of congestive heart failure. Keil states:

It seems probable that the area of distribution of these verrucae and the manner in which they are deposited contribute but little to the signs and symptoms in this disease. Most of the audible murmurs are, in all likelihood, attributable to extraneous factors, except in the relatively uncommon cases in which old valvular changes are encountered. The simultaneous occurrence of a pericardial rub makes the existence of gross endocardial involvement more probable as these two parts of the cardiac structure are often concurrently affected, but this rule has exceptions.

The diagnosis of disseminated lupus is usually made from the nature of the constitutional symptoms and the appearance of characteristic cutaneous lesions or signs of visceral disturbances. The diagnosis of Libman-Sacks syndrome may be suspected if signs of pericarditis and endocarditis appear but must be verified by postmortem examination. No adequate treatment is known, and the prognosis is uniformly bad.

*Hiatus Esophageal Hernia.*—Jones <sup>71</sup> has made a study of 128 patients with hiatus hernia, particularly from the standpoint of comparing the symptomatology in these patients with the symptomatology in patients suffering from heart disease. This group represented selected material only in that definite information regarding the size of the hernia was required and that only those patients were included whose presenting symptoms were referable to the hernia. The average age was 55. Concomitant diagnoses of heart disease (22) and biliary tract disease (22) were made for 44 patients. However, of the 22 patients with complicating

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70. (a) Keil, H.: Dermatomyositis and Systemic Lupus Erythematosus, Arch. Int. Med. 66:110 (July) 1940. (b) Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? New England J. Med. 225: 433, 1941.

71. Jones, C. M.: Hiatus Esophageal Hernia, New England J. Med. 225:963, 1941.

heart disease, Jones considered that only 11 had symptoms which might have contributed to the presenting symptomatology. Of the 128 patients, 91 had small hernias and 37 had large ones.

He found that substernal pain was experienced by over one third of the 91 patients with small hernias but occurred in only 5 of the 37 with large hernias. Shoulder pain, usually on the left, was noted by about one fourth of all the patients and radiation of pain into the arm by 12. Epigastric pain was noted by over 50 per cent of the patients. The records of 50 patients were sufficiently detailed to permit careful analysis of the pain. Twenty-five of the 50 patients complained of substernal pain, and 8 of these stated it was frequently, though not invariably, initiated by exercise, and 12 stated that emotional experiences frequently caused the pain to appear. As many as 15 of the 25 patients found that food, particularly a large meal, was responsible for initiating pain. Glyceryl trinitrate frequently afforded relief to 8 of the 25 patients complaining of substernal pain, but Jones emphasizes that in no case was the relief as regular as that noted in typical angina pectoris. Atropine or belladonna often afforded striking relief. Dyspnea was a frequent symptom in Jones's group and occurred in about one third of the patients with large hernias and one tenth of those with small ones. Palpitation was an occasional symptom.

Jones discusses the probable mechanism of causation of symptoms in these cases and concludes that when the hernia is large actual displacement of the heart and lungs may produce symptoms. A good example of this has recently been reported by McGinn and Spear.<sup>72</sup> Jones also believes it is logical to assume that the discomfort or pain is often secondary to intraesophageal or intragastric disturbances with typical referred pain and that the stimulus is mediated over visceral afferent fibers supplying the stomach or esophagus or over the sensory afferent fibers from the diaphragm.

We would like to emphasize the fact that both hiatus hernia and coronary heart disease may occur in the same patient, both being found in older persons, and in such patients they may be present together.

*Thrombi in the Heart.*—Garvin<sup>73</sup> studied the clinical and pathologic records of 771 consecutive autopsied patients who died of heart disease as to the occurrence of mural thrombi and infarction. Of the 771 patients, 265, of 34.4 per cent, had one or more mural thrombi. Thrombi were found in two thirds of the patients in whom myocardial infarction was present and in about one third of the patients with coronary artery disease without myocardial infarction or hypertensive or rheumatic

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72. McGinn, S., and Spear, L. M.: Diaphragmatic Hernia Presenting the Clinical Picture of Acute Cor Pulmonale, *New England J. Med.* **224**:1014, 1941.

73. Garvin, C. F.: Mural Thrombi in the Heart, *Am. Heart J.* **21**:713, 1941.

heart disease. The incidence of mural thrombi was high (40-47 per cent) in patients with hypertensive and with coronary heart disease complicated by various other types of heart disease. The incidence was low in patients with cor pulmonale and with subacute bacterial endocarditis. In patients with rheumatic heart disease mural thrombi occurred two and one-half times as often when auricular fibrillation was present. In patients with hypertensive heart disease the incidence of mural thrombi was three times as high in those below 40 as in those above 60. In rheumatic heart disease the incidence of mural thrombi was much higher in the older patients.

Garvin<sup>74</sup> also studied the same group of patients with respect to mural thrombi and infarction of various viscera. He found that pulmonary infarction was almost three times as frequent in those patients with mural thrombi in the right side of the heart as in those without thrombi in this location. Also, infarcts of the brain, kidneys, spleen, intestines and/or extremities were more than twice as common in patients with mural thrombi in the left side of the heart as in those without thrombi in this area.

270 Commonwealth Avenue.

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74. Garvin, C. F.: Mural Thrombi in the Heart as a Source of Emboli, *Am. J. M. Sc.* **201**:412, 1941.

## News and Comment

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**Announcement of Fellowships in Medicine and Public Health.**—The Commonwealth Fund of New York, a philanthropic foundation established in 1918 by the late Mrs. Stephen V. Harkness, announces that it is offering through the Pan American Sanitary Bureau fifteen fellowships for one year's study of public health subjects or postgraduate medical courses to properly qualified persons who are citizens of the other American republics. Fellowships in public health will be open to physicians, sanitary officers, technicians, public health nurses, etc. Fellows will be selected through a system of cooperation with medical and health authorities of the different countries concerned, and whenever it is deemed advisable they will be interviewed by traveling representatives of the Pan American Sanitary Bureau. Each fellowship will provide living allowances while the holder is in the United States, travel costs and tuition. Knowledge of the English language and the possession of certain specific qualifications will be among the requirements.

Application blanks giving complete information will be available through the Commonwealth Fund, 41 East Fifty-Seventh Street, New York; the Pan American Sanitary Bureau, Washington, D. C., or chiefs of American Missions in Latin America.

**Proceedings of the Federation of American Societies for Experimental Biology.**—The Federation of American Societies for Experimental Biology, composed of the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists, began publication of the federation proceedings in 1942.

Four issues will be published annually. Each year the March issue will contain the complete program of the scientific sessions of all the component societies as prepared for the forthcoming annual meeting of the federation, with abstracts of all scientific papers to be presented; the June and the September issue will contain the full text of twenty or more papers presented at the annual meeting, including probably the papers on the joint society program and papers of several society symposiums, and the December issue will contain material pertinent to the membership of the federation, i. e., the officers and a membership list, together with an index of the completed volume.

The subscription price is \$4 (\$4.75 foreign), payable in advance. Subscriptions should be sent to Dr. D. R. Hooker, Managing Editor, 19 West Chase Street, Baltimore.

**Eighth Annual Meeting of the Mississippi Valley Medical Society.**—The eighth annual meeting of the Mississippi Valley Medical Society will be held in the Hotel Lincoln-Douglas, Quincy, Ill., September 30 and October 1 and 2. The program will be given by twenty-five clinician teachers who will present over forty lectures, demonstrations, instructional courses, etc. On September 30 there will be a series of instructional courses by Kansas City clinicians and a complimentary stag supper. On October 1 a group of well known Chicago teachers will have charge. A special physicians' sports event program will be featured on

this date, with prizes for golf, skeet, bowling, archery and horseshoes. The banquet will be addressed by Dr. Edward H. Cary, of Dallas, Texas, past president of the American Medical Association, and the presidents of the state medical societies of Illinois, Iowa and Missouri. There will be numerous technical and scientific exhibits. Every ethical physician is cordially invited to attend, and no registration fee will be charged physicians in the uniforms of the armed forces of the United States. The complete program will appear in the September issue of the *Mississippi Valley Medical Journal*, and further information may be secured from the secretary of the society, Harold Swanberg, M.D., W. C. U. Building, Quincy.

**Meeting of the Medical Editors at Quincy, Ill., September 30.**—The second annual meeting of the Mississippi Valley Medical Editors' Association will be held at the Hotel Lincoln-Douglas, Quincy, Ill., the evening of Wednesday, September 30. This will be a dinner meeting under the leadership of Dr. Clyde P. Dyer, of St. Louis, editor of the *St. Louis County Medical Bulletin* and president of the Mississippi Valley Medical Editors' Association. All past and present medical editors and those persons interested in medical journalism or medical writing are cordially invited to attend. There is no registration fee. The program of the meeting or dinner reservations may be secured through Dr. Harold Swanberg, secretary of the association, W. C. U. Building, Quincy.

**American Association for the Advancement of Oral Diagnosis.**—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be "The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

## Book Reviews

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**Arthritis and Allied Conditions.** By Bernard I. Comroe, A.B., M.D., F.A.C.P.  
Second edition Price, \$9. Pp. 878. Philadelphia: Lea & Febiger, 1941.

The appearance of a second edition of Comroe's book on arthritis a short time after the publication of the first edition attests to the value of the work. It apparently has been well liked by the reading medical world and has proved of worth to students, to practitioners and to specialists in the field of arthritis. It is rather refreshing, parenthetically, to have a book of this character emanating from the pen of a man who is fundamentally an internist rather than an orthopedist.

The new edition has undergone a complete revision. Although arthritis seems to be more or less of a static condition, a considerable number of new thoughts, suggestions and practices have evolved in the last few years, all of which are incorporated and discussed in the book. Incidentally, forty additional illustrations have been added to the volume.

This new edition follows closely the general plan of the first edition. Three introductory chapters deal with the general features of arthritis, and then follows a series of chapters on rheumatoid (atrophic) arthritis. Starting at page 59, rheumatoid arthritis in all its many aspects, although largely treatment, occupies nearly the next three hundred pages. To degenerative joint disease (osteoarthritis) are assigned two chapters. Succeeding this are divisions devoted to spondylitis, fibrositis, radiology, rheumatic fever, gonorrheal arthritis, tuberculosis and syphilitic joint disease, traumatic arthritis and gout, as well as several others. Chapter 43 deals with the painful shoulder, really by no means an expression of arthritis, but nevertheless it does seem appropriate to incorporate it in this book, as well as chapters 44 and 45, on painful feet and on backache. The last chapter of the book deals with the sulfanilamide compounds. There is a question in the mind of the reviewer whether there is any necessity of incorporating such a chapter in a book devoted to arthritis; certainly extremely rarely is there any indication for the administration of one of these compounds in the treatment of arthritis, surely not of the ordinary and common form of the disease to which so many chapters are devoted. One other criticism that might seem legitimate is the rather poor arrangement of the chapters. It might be advisable to put the ones on radiology and arthritis, the organization of a clinic for arthritic patients and several others in the early part of the book, which represents a more or less general discussion of the problems of arthritis, then systematically follow through with those devoted to the various types of the disease. In discussing the treatment of rheumatoid arthritis the author gives the usual physical method of treatment, then adds a chapter which has to do largely with the use of neoarsphenamine, acetylsalicylic acid and iodides and the treatment of associated anemia; then follows a chapter on vaccines, succeeded by one on the orthopedic management of arthritis, which certainly should be incorporated with the discussion of physical measures.

The book, even if not well organized, is carefully and thoughtfully written. The illustrations are commendable, and the boxed incorporated summaries are advantageous to students or to rapid readers. The format of the book is excellent, as would be expected from its publishers.

**La enfermedad reumatica.** By Domingo Urrutia M. and Samuel Vaisman B.  
Pp. 191, with graphs, diagrams, photomicrographs and electrocardiograms.  
Santiago de Chile: La Sud-America, 1941.

The impetus initiating this monograph was derived from a realization that rheumatic heart disease is an enormous public health problem. The authors are members of the department of clinical medicine of the University of Chile, and it was published under the auspices of the Direccion General de Sanidad y El Departamento Central de Madre y Nino.

The monograph is written principally for practitioners of medicine in Chile, particularly for those in the remote provinces. It is an orderly discussion of rheumatic heart disease, starting with its social significance and relating the etiology, the pathology, the clinical aspects, the laboratory data and the treatment of the disease.

In preparing their discussion the authors have reviewed and briefed most of the recent publications on the subject. Their main sources have been from the United States of America and Great Britain, though some are from Germany, France and South America. In all, they reviewed seventy-one publications. They also have included their own observations based on a series of 285 rheumatic children treated during the last five years by the department of student health of the University of Chile, 5,000 students treated during the last five years in Santiago and on 430 hospitalized patients treated over a ten year period in the university, as well as a review of 13,144 autopsy reports compiled since 1919 by members of the pathology department of the university.

It is interesting to note that their results to date closely simulate those reported from similar latitudes in the northern hemisphere.

The monograph is bound in paper; reading is facilitated by large type, titles and subtitles in bold-faced print and a résumé in bold-faced print at the end of each chapter.

**Acute Alcoholic Intoxication: A Critical Review.** By Henry W. Newman, M.D. Price, \$2.50. Pp. 207. Stanford University, P. O., Calif.: Stanford University Press, 1941.

Dr. Henry W. Newman, assistant professor of medicine (neuropsychiatry) of Stanford University Medical School, is well qualified to discuss the problem of acute alcoholic intoxication, as shown by his numerous publications on this subject during the past ten years.

The book is not intended to review in detail all of the literature but instead is designed to present the major contributions of the last few years which add to the scientific and fundamental understanding of the subject.

The contents are divided into two parts; the first deals with the general actions of ethyl alcohol, namely, the absorption and distribution, the excretion and the combustion of this substance. This section brings together many scattered reports from the literature and presents them as individual points of view.

The second part deals with the toxicology of ethyl alcohol, namely, the acute toxicity of this substance, the chemical diagnosis of drunkenness and the treatment of acute alcoholic intoxication. This section, perhaps the most valuable part of the book, presents the results of work on many original problems which have practical value in the medicolegal practice of medicine. The practical application of tests for drunkenness is described in detail. The research concerning the problem of acute intoxication and that concerning the operation of motor vehicles was carried out by the author in collaboration with the California Department of Motor Vehicles in an effort to improve legislation regarding drunken driving.

The book contains a compilation of original work done by the author and other investigators. Their experimental results are presented, and the conclusions are left for the reader to draw.

**Personality and Mental Illness.** By John Bowlby, M.D. Price, \$2.75. Pp. 288, with charts. New York: Emerson Books, Inc., 1942.

This interesting study deals with personality traits which when exaggerated lead to recognizable psychotic states. The author's point is that psychoses are more quantitative than qualitative deviations from a person's previous status. The material is well handled and written in excellent style; it makes interesting and convincing reading.

## MORTALITY IN DIABETIC COMA

MORRIS F. COLLEN, M.D.

BERKELEY, CALIF.

Mortality statistics of diabetic coma at the Los Angeles County General Hospital are here presented and analyzed in an attempt to evaluate the importance of the various factors which influence the mortality of such coma.

The data were compiled from all consecutive cases of diabetic coma encountered in this hospital from 1930 through 1940. Included were only those cases in which were present (1) an elevated level of blood sugar, (2) a low carbon dioxide-combining power and (3) clinical symptoms of diabetic coma, with definite signs of mental depression. This series totaled 315 cases of coma in 274 diabetic patients. Coma occurred twice in 16 patients, three times in 5 patients, four times in 1 patient and seven times in 2 patients.

### GROSS MORTALITY STATISTICS

As has been emphasized by many observers,<sup>1</sup> the gross mortality of diabetic coma has little comparative value, since so many variable factors are involved in determining the severity of coma in an individual patient. No 2 cases or series of cases can be directly compared unless they represent attacks of approximately equal severity.

Table 1 presents gross mortality statistics from six series of cases. Since the cases in the various series do not necessarily represent episodes

Dr. Solomon Strouse contributed assistance, criticisms and suggestions during the preparation of this paper.

From the Department of Medicine, College of Medical Evangelists, and Los Angeles County General Hospital.

1. (a) Baker, T. W.: Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, *Arch. Int. Med.* **58**:373-406 (Sept.) 1936. (b) Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Joslin, A. P.: Diabetic Coma, *ibid.* **59**:175-195 (Feb.) 1937. (c) Dillon, E. S., and Dyer, W. W.: Factors Influencing the Prognosis in Diabetic Coma, *Ann. Int. Med.* **11**:602-617, 1937. (d) Rabinowitch, I. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma, *ibid.* **12**:1403-1428, 1939. (e) Owens, L. B., and Rockwern, S. S.: Prognosis in Diabetic Coma: Basic Importance of Mental State, *Am. J. M. Sc.* **198**:252-260, 1939.



of equal severity, these gross statistics are of little value in indicating success in treatment. The purpose of this study is to determine what variables are important in estimating the severity of coma and to derive a method for directly comparing cases under identical conditions.

#### PRECIPITATING FACTORS

The factors which could be considered responsible for precipitating the attacks of coma in this series of cases were studied. The precipitating

TABLE 1.—*Gross Mortality Statistics*

Hospital	No. of Cases	No. of Deaths	Mortality, %
Mayo Clinic (1936) <sup>1a</sup> .....	168	17	15.7
New England Deaconess Hospital (1937) <sup>1b</sup> .....	318	38	11.9
Philadelphia General Hospital (1937) <sup>1c</sup> .....	263	117	43.7
Montreal General Hospital (1939) <sup>1d</sup> .....	123	33	26.4
Cincinnati General Hospital (1939) <sup>1e</sup> .....	92	47	51.0
Los Angeles County General Hospital (1940).....	315	105	33.3

TABLE 2.—*Precipitating Factors*\*

A. Infections .....	182 (54.0%)
1. Infection of the respiratory tract.....	105
(a) Infection of the upper respiratory tract.....	64
(b) Pneumonia .....	27
(c) Tuberculosis .....	7
(d) Otitis media .....	7
2. Acute gastrointestinal upsets.....	28
3. Subcutaneous abscesses, etc. ....	24
4. Foot infections, gangrene.....	12
5. Pyelitis, pyelonephritis .....	6
6. Miscellaneous .....	7
B. Dietary infractions or omission of insulin.....	77 (22.6%)
1. Insufficient insulin .....	43
2. Dietary indiscretions (?).....	18
3. No treatment prior to coma.....	16
C. Miscellaneous factors .....	14 (4.1%)
D. No recorded factor.....	61 (19.0%)

\* Twenty-two cases in which the patients were in diabetic acidosis but were mentally alert were included in this table only.

factor in a case of diabetic coma was considered to be a definite recent illness, a disturbance in a patient's dietary or insulin regimen or other immediate unusual event in his history, with subsequent appearance of symptoms of coma.

As shown in table 2, in 54 per cent of all cases coma was precipitated by infections, the great majority of which affected the respiratory tract.

Insulin insufficiency was the second most common precipitating factor of coma, due either to complete cessation of insulin or administration of sufficient doses.

Acute gastrointestinal upsets included dysenteries, food poisonings, etc., but in many cases it was difficult to determine whether a gastrointestinal upset precipitated the coma or whether it was the first symptom of coma.

Dietary indiscretion as the precipitating agent was probably not as important a factor as the table would indicate. Careful study of the histories in each of the 18 cases so classified proved it difficult to determine whether pure dietary or carbohydrate excess was the primary causative agent. In 4 cases the onset of coma was associated with acute alcoholism. In the remaining ones the history was not incompatible with mild food poisoning, acute gastritis or simple acute gastrointestinal upset. The question of associated insufficient insulin dosage as a contributing factor could not be ruled out in many instances. Critical analysis indicated that although in the 18 cases coma was precipitated by unusual or excessive food intake, in none could it be

TABLE 3.—*Time of Death*

After entry.....	1 Hr.	2-5 Hr.	6-12 Hr.	13-24 Hr.	25-36 Hr.	37-48 Hr.	49-72 Hr.	73-96 Hr.	5-7 Days	8-14 Days
Number of deaths.....	4	11	24	24	13	8	6	5	2	3

directly attributed to pure carbohydrate excess. It has been the contention of Mirsky and co-workers<sup>2</sup> that excessive carbohydrate ingestion is not a precipitating cause for diabetic coma.

Coma was the mode of onset of diabetes in 16 cases. Five per cent of comas occurred in patients who were unaware of previous diabetes.

Foot infections and gangrene as the precipitating factors occurred predominantly in the older age groups.

#### TIME OF DEATH AFTER ADMISSION TO HOSPITAL

How soon a patient died after admission to the hospital tends to indicate to some degree the severity of coma on admission. It is noted in table 3 that 48 per cent of fatalities occurred six to twenty-four hours after entry into the hospital. Four per cent of deaths occurred within one hour after admission, the condition obviously being terminal on entry. Five per cent of deaths occurred after four days from complications, not from diabetic coma per se.

2. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, *J. Clin. Endocrinol.* 1:307-315, 1941.

CHRONOLOGIC DISTRIBUTION

Table 4 presents the percentage mortality of diabetic coma according to years. It is noted that the average percentage mortality in all cases from 1930 through 1934 was 41.7 per cent. During this period patients in diabetic coma were admitted to various wards throughout the hospital. In May 1934 two wards for diabetic patients were inaugurated, and all such patients have since been segregated in these wards, under

TABLE 4.—*Chronologic Distribution*

Year	No. of Cases	No. of Deaths	Mortality, %
1930.....	15	8	53.3
1931.....	12	3	25.0
1932.....	27	9	33.3
1933.....	41	19	46.3
1934.....	8	4	50.0
1930-1934.....	103	43	41.7
1935.....	18	4	22.2
1936.....	27	7	25.9
1937.....	37	13	35.1
1938.....	42	16	38.1
1939.....	44	12	27.3
1940.....	44	10	22.7
1935-1940.....	212	62	28.3
1930-1940.....	315	105	33.3

TABLE 5.—*Seasonal Distribution*

Month	Number of Cases	Number of Deaths	Mortality, %	Infections
January.....	28	8	29.6	14
February....	26	11	42.3	12
March.....	24	10	41.6	14
April.....	25	11	44.0	15
May.....	21	7	33.3	8
June.....	20	6	30.0	10
July.....	32	9	28.1	14
August.....	23	6	26.1	13
September....	29	6	20.7	12
October.....	30	11	36.7	15
November.....	22	9	40.8	9
December.....	35	10	28.8	18

the supervision of attending and resident physicians especially interested in diabetes mellitus. Probably as a result of this specialized care, the average percentage mortality from 1935 through 1940 was 28.3 per cent. The gross average mortality in 315 cases of diabetic coma from 1930 through 1940 was 33.3 per cent.

SEASONAL DISTRIBUTION

A study of the cases according to the month in which the patients were admitted for coma revealed (table 5) that their distribution throughout the twelve months was quite uniform, the greatest incidence

being in December. Baker<sup>1a</sup> and Joslin and associates<sup>3</sup> have found coma to be most frequent in August. When the cases with associated infection were plotted by months (table 5), the greatest incidence of infection was also found to be in December. There was a close relation between incidence of coma and incidence of associated infection.

A striking variation of mortality with season was also demonstrated in table 5. A low mortality of about 29 per cent occurred in December and January, rising to a high of 44 per cent in April, then decreasing to a second low of 20.7 per cent in September and again rapidly rising to a second high peak of 40.8 per cent in November. The two high peaks of mortality in spring and late fall are clearly shown in figure 1. Although it was observed that a close relation existed between monthly incidence of coma and associated infection, no relation was noted between monthly incidence of infection in diabetic coma and mortality. Likewise,

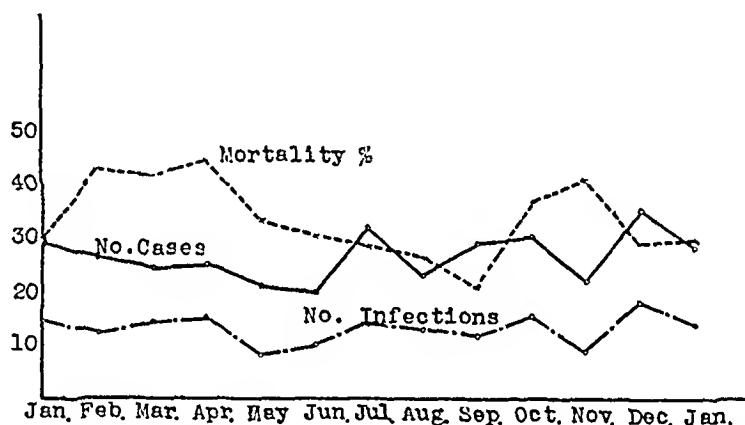


Fig. 1.—Monthly distribution of mortality of diabetic coma, incidence of coma and incidence of infections in 315 cases of diabetic coma.

study of the original data revealed that the number of deaths in each individual month was evenly distributed throughout the years, so that the peak in November, for example, was not due to an epidemic of deaths in any one year.

#### RELATION OF MORTALITY TO SEX

As shown in table 6 the average mortality for the two sexes was equal. It is interesting to note that in almost two thirds of the cases of coma the patients were women; this greater frequency has also been demonstrated by other observers.<sup>1</sup>

Owens<sup>1e</sup> stated that coma occurs more frequently during the decade of puberty and of menopause, with higher mortality in the female in

3. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Hunt, H. M.: Diabetic Coma, *M. Clin. North America* 16:793-827, 1933.

these periods. Table 6 confirms the observation that coma apparently was more prone to occur during the puberal and the climacteric period, but mortality was not higher in the female.

#### RELATION OF MORTALITY TO AGE

The oldest patient was an 85 year old woman, who died of complicating empyema of the gallbladder and pneumonia. The oldest patient to recover was a 75 year old man whose blood contained 832 mg. of sugar per hundred cubic centimeters and had a carbon dioxide-combining power of 13 volumes per cent. The youngest patient was 6 years old.

TABLE 6.—*Interrelation of Sex, Age and Mortality*

Age, Yr.	Males			Females		
	Number of Cases	Number of Deaths	Mortality, %	Number of Cases	Number of Deaths	Mortality, %
0-9	6	1	16.6	6	2	33.3
10-19	21	3	14.3	44	2	4.5
20-29	22	6	27.3	30	9	30.0
30-39	18	4	22.2	25	7	28.0
40-49	25	11	44.0	33	12	36.4
50-59	14	7	50.0	28	17	60.8
60-69	6	4	66.6	22	8	36.3
70+	6	4	66.6	9	8	89.0
Total	118	40	33.9	197	65	33.0

TABLE 7.—*Relation of Mortality to Age*

Age, Yr.	Number of Cases	Number of Deaths	Mortality, %
—15.....	46	6	13.0
16-30.....	85	14	16.5
31-50.....	105	41	39.0
51-70.....	65	33	50.7
71+.....	14	11	78.6

The largest group of cases represented patients between 30 and 50 years of age.

Table 7 shows the relation of mortality to the age of a patient. As the age of the patient increases, the mortality increases in a direct relation. Patients 80 years of age had roughly about twice the mortality of patients 40 years of age, who in turn had approximately twice the mortality of patients 20 years of age. The age of the patient, therefore, is obviously an important factor in influencing the severity of diabetic coma.

#### RELATION OF MORTALITY TO DURATION OF COMA

The length of time a patient had been in coma was not always definite but was estimated from the time at which the patient definitely

became drowsy. The longest duration of coma before admission to the hospital was ninety-six hours, as observed in 6 cases. The duration of coma is usually considered an important factor in determining the prognosis, and table 8 indicates that this is true to a certain degree; however, previous observers have not analyzed the relation in adequately small periods over a sufficient time. It was noted that the mortality rose rapidly as duration of coma approached twenty-four hours, then reached a plateau from twenty-five to forty-eight hours, after which the percentage mortality actually dropped. As has been demonstrated elsewhere,<sup>4</sup> untreated patients in coma and still alive after forty-eight hours not only had a lower average mortality, but had a less severe degree of acidosis.

TABLE 8.—*Relation of Mortality to Duration of Coma*

Hours	Number of Cases	Number of Deaths	Mortality, %
—12.....	184	43	23.4
13-24.....	62	26	41.9
25-36.....	2	1	50.0
37-48.....	17	9	53.0
49+.....	15	5	33.3
Unknown.....	35		

TABLE 9.—*Relation of Mortality to Degree of Unconsciousness*

Degree of Unconsciousness	Number of Cases	Number of Deaths	Mortality, %
Drowsy.....	85	5	5.9
Semiconscious.....	93	20	21.5
Unconscious (responds to painful stimuli)....	106	54	51.0
Completely unconscious.....	31	26	83.8

## RELATION OF MORTALITY TO DEGREE OF UNCONSCIOUSNESS

Table 9 shows that as the degree of mental depression increased, the mortality increased proportionately. Patients admitted in uncomplicated diabetic "coma" who were alert and conscious had a mortality of zero in this hospital. As has been emphasized by Rabinowitch and associates<sup>1d</sup> and borne out by this series of cases, alert patients in a state of diabetic acidosis should not be classified as being in coma. No case in which a patient was alert or conscious was included in this series. Patients admitted completely unconscious and not responding to painful stimuli, such as corneal touch or supraorbital pressure, had the high mortality of 83.8 per cent. Thus the degree of unconsciousness of a patient is an important factor in determining the severity of coma.

4. Collen, M. F.: Interrelation of the Factors Influencing Mortality in Diabetic Coma: A Statistical Study, *Arch. Int. Med.*, this issue, p. 369.

## RELATION OF MORTALITY TO BLOOD PRESSURE

Although it is a well known fact that the mortality of diabetic coma is closely related to blood pressure, few writers have included blood pressure among those factors of greatest importance in determining ultimate prognosis.<sup>5</sup> Previous attempts to estimate the importance of blood pressure in grading severity of coma have been based only on systolic blood pressure.<sup>1d</sup> Table 10 *A* shows that when systolic blood pressure was over 90 mm. of mercury, the average mortality was 27.6 per cent. When the systolic blood pressure fell to shock levels, i. e.,

TABLE 10.—*Relation of Mortality to Blood Pressure*

A Systolic Blood Pressure, Mm. Hg	Number of Cases	Number of Deaths	Mortality, %
90+..	210	58	27.6
89 80.	18	13	72.2
79-70.	7	4	57.2
69 60	2	2	100.0
59-50	4	4	100.0
49—	17	14	82.3
B Diastolic Blood Pressure, Mm. Hg			
80+.	105	25	23.8
79 70.	50	13	26.0
69 60.	42	13	31.0
59 50. .	21	12	57.1
49 40..	10	8	80.0
39—..	28	23	82.2
Unknown	59		
C Pulse Pressure, Mm. Hg			
60+.	49	17	34.7
59 40	83	24	28.6
39 30..	50	20	39.0
29 20..	27	9	33.3
19—	14	13	92.8

under 90 mm. of mercury, the mortality immediately rose to over 72.2 per cent. Groups in which the blood pressure values ranged from 79 to 50 mm. of mercury were combined because of the small number of cases. It is obvious that the systolic blood pressure is valuable only in classifying severity of coma in two kinds of patients: (1) those in shock, with an average mortality of about 75 per cent, and (2) those not in shock, with an average mortality of about 28 per cent.

Physiologically, the diastolic blood pressure is a better measure of shock than the systolic blood pressure, and table 10 *B* bears out this point. It is evident that as the diastolic blood pressure fell, the mortality

5. (a) Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1940. (b) Owens and Rockwern.<sup>1e</sup>

correspondingly rose in an almost direct relation. The diastolic blood pressure has a much closer quantitative relation to percentage of mortality than the systolic blood pressure and is therefore an important factor influencing the mortality of diabetic coma.

To determine whether the pulse pressure had an effect on mortality table 10 C was prepared. Mortality was independent of pulse pressure until the pulse pressure fell below 20 mm. of mercury to obvious shock levels; then the mortality immediately jumped from 33 to 92.8 per cent. Pulse pressure confirms and bears out the important effect of shock on mortality but is of no value as a quantitative yard stick with which to measure severity of coma.

#### RELATION OF MORTALITY TO BLOOD SUGAR

Although it is usually stated that the mortality of diabetic coma is not dependent on the degree of hyperglycemia, it has been shown by

TABLE 11.—*Relation of Mortality to Blood Sugar*

Sugar, Mg./100 Cc.	Number of Cases	Number of Deaths	Mortality, %
—299.....	25	2	8.0
300-499 . . . . .	99	23	23.2
500-799... . . . .	136	52	38.2
800-999.. . . . .	36	18	50.0
1,000+.. ....	19	10	52.6

various observers<sup>1d</sup> that there is a definite rise in mortality with higher values of blood sugar. This is also confirmed by the present study (table 11), which shows a definite rise in mortality as blood sugar rises, leveling off at an average mortality of about 50 per cent with blood sugar values over 800 mg. per hundred cubic centimeters. The highest level of blood sugar in this series was 1,334 mg. per hundred cubic centimeters, in a patient who died in shock thirty-six hours after admission. The highest level of blood sugar in a patient who recovered was 1,332 mg. per hundred cubic centimeters, in a 12 year old boy, admitted unconscious, with duration of coma under twelve hours, no blood pressure obtainable and a carbon dioxide-combining power of the blood of 22 volumes per cent on admission. The highest value reported for blood sugar in a case of nonfatal coma was 1,850 mg. per hundred cubic centimeters.<sup>6</sup>

6. Dillon, E. S., and Dyer, W. W.: Diabetic Coma with Extreme Hyperglycemia, *Am. J. M. Sc.* **190**:683-686, 1935.



RELATION OF MORTALITY TO THE CARBON DIOXIDE-  
COMBINING POWER OF THE BLOOD

It has long been believed that the carbon dioxide-combining power of the blood is a measure of the severity of diabetic coma. In fact, Joslin and associates <sup>1b</sup> established a carbon dioxide-combining power of the plasma of 20 volumes per cent as the arbitrary dividing line between coma and precoma. However, reference to table 12 indicates that in cases in which the carbon dioxide-combining power is more than 20 volumes per cent the mortality is as high as in cases in which the carbon dioxide-combining power is 10 volumes per cent. The average mortality in all cases in which the carbon dioxide-combining power of the blood was 20 volumes per cent or over was 33.3 per cent; the average mortality in all cases in which this factor measured 19 volumes per cent or under was exactly the same, namely,

TABLE 12.—*Relation of Mortality to the Carbon Dioxide-Combining Power of the Blood*

Carbon Dioxide, Vol. %	Number of Cases	Number of Deaths	Mortality, %
20+.....	69	23	33.3
19-16.....	75	23	30.7
15-12.....	79	24	30.4
11-8.....	70	22	31.4
7-4.....	20	12	60.0
3-.....	2	1	50.0

33.3 per cent. In 69 (22 per cent of the entire series) the value for this factor was over 20 volumes per cent. On the basis of similar data, Dillon and Dyer <sup>1c</sup> included in their series all cases in which the carbon dioxide-combining power of the blood was 29 volumes per cent or below, and Baker <sup>1a</sup> included cases in which this factor measured 28 volumes per cent or below.

Rabinowitch and co-workers,<sup>1d</sup> citing a total of 713 cases of coma, showed conclusively that there is no relation between the carbon dioxide-combining power of the blood and mortality; in fact, they pointed out that the highest mortalities occurred in cases in which this factor was greater than 25 volumes per cent. The highest value in my series was 30 volumes per cent, in a 75 year old man, admitted without any history obtainable, completely unconscious and with a blood pressure of 80 mm. of mercury systolic and zero mm. of mercury diastolic, a blood sugar level of 715 mg. per hundred cubic centimeters and no complications; the patient died in shock six hours after admission; autopsy failed to disclose any abnormalities other than those consistent with uncomplicated diabetic coma. The lowest value for the carbon

dioxide-combining power of the blood in this series was 3 volumes per cent, in a 46 year old woman, admitted unconscious and with a blood pressure of 130 systolic and 80 diastolic measured in millimeters of mercury, a blood sugar level of 582 mg. per hundred cubic centimeters, blood nonprotein nitrogen level of 63 mg. per hundred cubic centimeters and a complicating infection of the upper respiratory tract; she responded to therapy but died two weeks later of pyelonephritis.

#### RELATION OF MORTALITY TO BLOOD NONPROTEIN NITROGEN

The highest value for blood nonprotein nitrogen in a case of uncomplicated diabetic coma was 156 mg. per hundred cubic centimeters, for a 48 year old woman, admitted semiconscious, in a coma of forty-eight hours' duration and with a blood pressure of 90 systolic and 60 diastolic measured in millimeters of mercury, a blood sugar level of 666 mg. per hundred cubic centimeters and a carbon dioxide-

TABLE 13.—*Relation of Mortality to Blood Nonprotein Nitrogen*

Nonprotein Nitrogen, Mg./100 Ce.	Number of Cases	Number of Deaths	Mortality, %
—40.....	43	9	20.9
41-60.....	35	13	37.1
61-80.....	22	13	59.0
81-100.....	14	7	50.0
101-120.....	4	3	75.0
121+.....	4	4	100.0
Unknown.....	193		

combining power of 28.6 volumes per cent; the patient died of anuria four days after admission; autopsy revealed a normal heart and normal kidneys; the diagnosis was severe azotemia due to uncomplicated diabetic coma.

Table 13 indicates a direct relation between mortality and degree of azotemia. In cases in which the value for blood nonprotein nitrogen were normal the average mortality was 20.9 per cent; in cases in which the values exceeded 121 mg. per hundred cubic centimeters the mortality was 100 per cent. Blood nonprotein nitrogen is an important factor in determining the severity of diabetic coma.

#### RELATION OF MORTALITY TO COMPLICATIONS

The mortality of diabetic coma rises with any complication. Table 14 *A* shows that the presence of an infection approximately doubled the mortality. On the other hand, a complication which was capable of causing death independent of the coma (table 14 *B*) more than quad-

rupted the mortality. More detailed study of the relation between complications and mortality is shown in table 14 C. This table includes complications of all types, in which the severity of the complication was estimated and graded from 1 (very mild) to 5 (very severe). It is evident from table 14 C that complications occurred in over half (56 per cent) of the cases of coma. The average mortality in cases of uncomplicated coma in this series was 22.8 per cent; that in cases of complicated coma rose in direct proportion to the severity of the complication, very severe complications (grade 5) having 90.8 per cent mortality. The two groups of cases in which complications were mild (grades 1 and 2) predominantly represented infections of the respiratory tract

TABLE 14.—*Relation of Mortality to Complications*

	Number of Cases	Number of Deaths	Mortality, %
<b>A. Relation of Mortality to Infections</b>			
Infection absent . . . . .	163	40	24.5
Infection present . . . . .	152	65	42.0
<b>B. Relation of Mortality to Acute Associated Diseases Capable of Causing Death Inde- pendent of Coma</b>			
Disease absent . . . . .	220	37	16.8
Disease present . . . . .	95	68	71.5
<b>C. Relation of Mortality to Complications of All Types</b>			
Severity of complication			
None.....	135	31	22.8
1... ..	78	8	10.2
2.....	11	2	18.2
3 . . . . .	18	5	27.8
4 .... .	16	10	62.5
5 ... ..	54	49	90.8

in younger age groups. This age factor explains the lower average mortality in groups in which complications were mild than in the group without uncomplications comprising all ages. Although the estimation of the severity of a complication is arbitrary, requiring much clinical judgment, it is evident from this series of cases that the percentage mortality is directly proportional to the severity of the complication. The presence of a complication is an important factor influencing the mortality of diabetic coma.

#### MISCELLANEOUS FACTORS

Patients in diabetic coma with coffee ground vomitus had an average mortality of 25 per cent in this series. The presence of hematemesis, therefore, does not have any great significance in prognosis.

Other studies<sup>7</sup> have shown that there is little relation between degree of leukocytosis and mortality. The great majority of patients in coma had white cell counts over 10,000 per cubic millimeter.

#### CAUSES OF DEATH

Analysis of the 105 deaths in this series revealed that in cases of uncomplicated coma 74.3 per cent of the patients died of shock. In cases of complicated coma only 36.6 per cent of the patients died of shock, while death in the remaining cases was due to associated diseases (most important of which were pneumonia 28.1 per cent, sepsis 15.5 per cent and cardiac failure 8.5 per cent). This indicates that the treatment of diabetic coma should be directed, first, toward the prevention of and treatment of shock, and, second, toward the correction of any associated disease.

#### ESTIMATION OF SEVERITY OF DIABETIC COMA

It has been shown that there are many factors which influence the severity of diabetic coma and the resulting mortality, namely, the age of the patient, the degree of unconsciousness, the blood pressure, the duration of coma, the blood nonprotein nitrogen, the blood sugar and the severity of complications. Theoretically, an ideal index of severity of diabetic coma would be one which would indicate that very mild forms (grade 1) would have practically zero mortality, moderately severe forms (grade 3) would have about 50 per cent mortality and very severe forms (grade 5) would have about 100 per cent mortality. In other words, there should exist a linear relation between mortality and severity index. Figure 2 demonstrates that if one grades the various factors from 1 to 5, in which grade 1 is very mild and grade 5 very severe and plot their relation to percentage mortality, using values obtained in tables 7 through 14, the factors fall into two groups. Those in figure 2 *A*, namely, the age of the patient, the degree of unconsciousness, the diastolic blood pressure, the severity of complications and the blood nonprotein nitrogen, all show almost a linear relation between the severity of the factor and the percentage mortality, approximating closely the theoretic "ideal" index. These factors obviously are important and dependable criteria for evaluating severity of coma. On the other hand, in figure 2 *B* it is evident that the systolic blood

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7. Dillon and Dyer.<sup>1c</sup> Rabinowitch.<sup>1d</sup>

pressure and the carbon dioxide-combining power of the blood can have little value in indicating the severity of coma, whereas the duration of coma and the height of blood sugar may have some limited value.

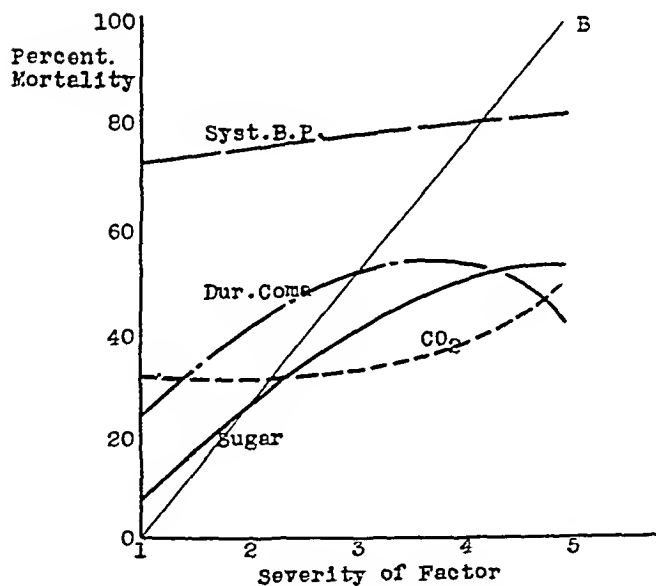
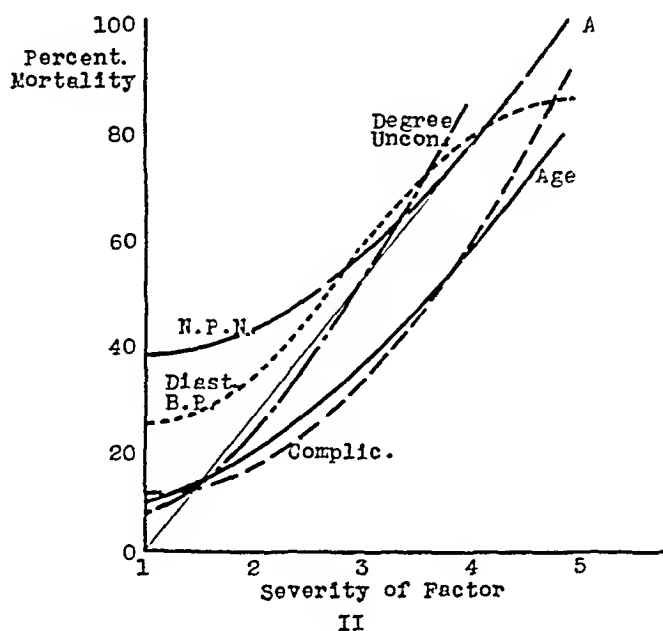


Fig. 2.—Relation between percentage mortality and the severity of various factors in diabetic coma.

#### DEVELOPMENT OF A SEVERITY INDEX OF DIABETIC COMA

It has been demonstrated that no single factor may be taken by itself as a reliable index of severity and prognosis in diabetic coma. For the purpose of determining a quantitative index for estimation of the

degree of severity of coma, so that mortality statistics of different series may be comparable, Rabinowitch and associates<sup>1d</sup> developed a "severity index" based on evaluation of the several variables, as shown in table 15. Grades of severity from 1 to 5 were assigned to each variable, and the combined use of all the variables gave an index of severity which the authors demonstrated to be superior to general clinical impression and estimation of severity. Although this is a marked advancement toward proper evaluation and comparison of cases, it was felt from this study that certain modifications of the Rabinowitch severity index were indicated.

In the present study age, degree of unconsciousness and blood non-protein nitrogen all were shown to have a direct relation to mortality;

TABLE 15.—*Calculation of Severity Index (Rabinowitch)*

Factor	Rating				
	1	2	3	4	5
Age, yr. ....	—15	16-30	31-50	51-70	71+
Duration of coma, hr. ....	—12	13-24	25-36	37-48	49+
Degree of unconsciousness. ....	Drowsy	Semi-conscious	Unconscious (but responds to pain)	.....	Completely unconscious
Coffee ground vomitus. ....	.....	.....	Present		
Infection .....	.....	.....	Present		
Blood pressure, systolic, mm. Hg	89-80	79-70	69-60	59-50	49—
Carbon Dioxide-Combining power, vol. %	19-16	15-12	11-8	7-4	3—
Nonprotein nitrogen, mg. per 100 Cc.	41-60	61-80	81-100	101-120	121+
Associated conditions (acute conditions capable of causing death independent of coma)	Very mild	Mild	Moderately severe	Severe	Very severe

these factors deserve the values assigned to them. With reference to duration of coma, Rabinowitch in his analysis failed to study this factor in twelve hour periods, as presented in table 8. This table and also figure 2 *B* indicate that duration of coma does not bear a direct relation to mortality, as does age, for example. A patient who has been in coma fifty hours does not deserve a rating five times that of a patient who has been in coma ten hours. Figure 2 *B* shows that patients in coma over twenty-four hours have a mortality of 40 to 50 per cent; it is felt, therefore, that patients in coma over twenty-four hours deserve a grade 3 of severity but no further separation is justifiable. Patients in coma under twenty-four hours do not deserve any grade, since too much "padding" of the lower indexes of severity results.

Cases in this series in which coffee ground vomitus was present had only 25 per cent mortality; this being below average mortality for

the entire series, the presence of hematemesis does not indicate a higher mortality and does not deserve an additional grade.

It has been shown in table 10 and figure 2*B* that diastolic blood pressure is a much more reliable index of severity than systolic blood pressure; it is therefore recommended that diastolic blood pressure be used in determining the severity index.

It has been indicated repeatedly in this discussion that the carbon dioxide-combining power of the blood has no relation to severity of coma; a patient with a value for this factor of 5 volumes per cent does not deserve a more severe grade than one with a value of 20 volumes per cent. It is concluded that there is no justification for including this factor in the calculation of the severity index.

TABLE 16.—*Modified Severity Index of Diabetic Coma*

Factor	Rating				
	1	2	3	4	5
Age, yr. ....	—15	16-30	31-50	51-70	71+
Diastolic blood pressure, mm. Hg	69-80	59-50	49-40	39-30	—27
Complication .....	Very mild	Mild	Moderately severe	Severe	Very severe
Blood nonprotein nitrogen, mg./100 cc.	41-60	61-80	81-100	101-120	121+
Degree of unconsciousness.....	Drowsy	Semi-conscious	Unconscious (responds to pain)	Completely unconscious	
Duration of coma, hr. ....	.....	.....	24+		
Blood sugar, mg./100 cc.....	.	. ..	800+		

In the Rabinowitch severity index consideration is given to complications of two types, infections and acute conditions capable of causing death independent of coma. The present series of cases indicated that patients with chronic heart disease have as high a mortality as patients with other acute conditions. Serious complicating chronic diseases are as important as acute conditions in influencing mortality. An additional grade 3 because the complication is an infection is not justified, for the same condition is graded twice; e. g., a patient with moderately severe gangrene of the foot, which is secondarily infected, would receive a grade 3 for an associated condition and a grade 3 for the presence of an infection, which would give him a total grade of 6 for complicating diseases; whereas a patient with a much more severe complication of massive cerebral hemorrhage receives only a grade of 5. It is recommended that all complications be placed in one group, as has been done in this series of cases. A patient with acute follicular tonsillitis has a very mild complication and receives a grade

of 1; a patient with moderately severe gangrene of a foot receives a grade of 3, and a patient with hypertensive heart disease and evidence of congestive heart failure receives a grade of 5. Such conditions as arteriosclerosis and latent syphilis are not considered as complications.

It has been shown in table 11 and figure 2 *B* that a definite relation exists between blood sugar and mortality. Figure 2 *B* indicates that a patient with a blood sugar value over 800 mg. per hundred cubic centimeters has a mortality of over 50 per cent. Such a value then deserves an additional grade of 3.

As a result of these studies a modification of the Rabinowitch severity index is proposed and is presented in table 16.

#### CALCULATION OF SEVERITY INDEX

Two examples of the method by which the index of severity is calculated are given:

##### Example 1:

Factor	Severity	Grade
Age of patient.....	30 yr.	2
Diastolic blood pressure.....	60 mm. Hg.	1
Severity of complication.....	None	0
Blood nonprotein nitrogen.....	65 mg./100 cc.	2
Degree of unconsciousness.....	Semiconscious	2
Duration of coma.....	15 hr.	0
Blood sugar .....	870 mg./100 cc.	3
		—
		Severity index 10

From figure 3 it is seen that a severity index of 10 gives this patient a prospective mortality of about 20 per cent, according to this series of cases.

##### Example 2:

Factor	Severity	Grade
Age of patient.....	60 yr.	4
Diastolic blood pressure.....	0 mm. Hg	5
Severity of complication.....	Gangrene and pneumonia	5
Blood nonprotein nitrogen.....	95 mg./100 cc.	3
Degree of unconsciousness.....	Complete	4
Duration of coma.....	15 hr.	0
Blood sugar.....	700 mg./100 cc.	0
		—
		Severity index 21

Figure 3 shows that the prospective mortality for this patient is 98 per cent.



## COMPARISON OF INDEXES

Of the entire series of cases, in only 107 were sufficient data available to calculate the severity index by the methods brought out. Table 17 presents the same 107 cases with severity indexes calculated both by the Rabinowitch and by the modified index. It is noted that the Rabinowitch index produces mortalities consistently low in the groups of cases of milder coma. There is not sufficient difference in mortality of patients with indexes below 10 to warrant separation; this is due to the "padding" of unnecessary factors in the groups of cases of milder coma and is eliminated in the modified index. This is better shown in figure 3, in which the mortality curves are plotted for both indexes.

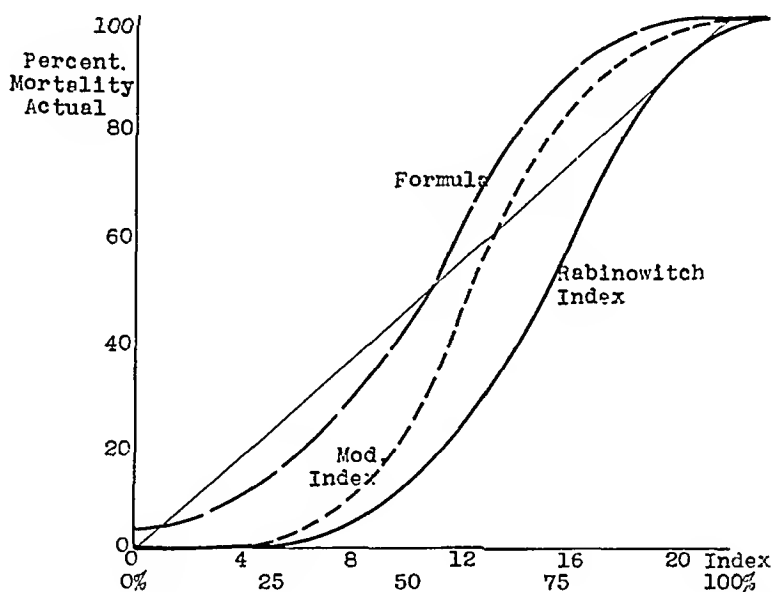


Fig. 3.—Comparison of actual mortality and calculated mortality in 107 cases of diabetic coma.

The "ideal" index would be a direct straight line relation between mortality and severity index. It is evident that the Rabinowitch index produces values too low and gives a curve which falls below the "ideal" in its entirety. The proposed modified index approaches more closely to the "ideal."

The modified severity index is recommended because (1) it is simpler, (2) it is theoretically more accurate and (3) it actually gives a more direct relation to mortality.

## DERIVATION OF A SEVERITY FORMULA

Further analysis of the modified severity index and of figure 2 suggested that a mathematical formula might be obtained representing

the relation between mortality and severity, thus further simplifying calculations.

As was pointed out in discussion of figure 2*A*, there is a direct relation between mortality and (1) the age of the patient, (2) the degree of unconsciousness, (3) the diastolic blood pressure, (4) the severity of complications and (5) the blood nonprotein nitrogen. Of less importance is the relation between mortality and the blood sugar and the duration of coma. To obtain a formula of greater simplicity for practical use, it is evident that both duration of coma and blood sugar are of secondary importance in estimating mortality. It has been shown elsewhere<sup>4</sup> that a direct linear relation exists between blood nonprotein nitrogen and diastolic blood pressure. Because of the direct quantitative relation between the two, one may be used to represent the other; to use both factors may give too much weight to the same primary influencing factor; therefore, blood nonprotein nitrogen may be repre-

TABLE 17.—*Comparison of Percentage Mortality Calculated with Severity Indexes and the Severity Formula*

Index	Rabinowitch Index			Modified Index			Severity Formula			
	No. of Cases	Deaths		No. of Cases	Deaths		Formula, %	No. of Cases	Deaths	
		No.	%		No.	%			No.	%
—5	2	0	0.0	12	0	0.0	—20	28	4	14.3
6-10	28	1	3.6	41	4	9.8	21-40	38	7	18.5
11-15	36	10	27.8	29	17	58.5	41-60	16	8	50.0
16-21	34	25	73.5	21	18	85.6	61-80	21	19	90.0
21+	7	7	100.0	4	4	100.0	81+	4	4	100.0

sented by diastolic blood pressure. Although there is a direct relation between age and complicating diseases, these two factors are still fundamentally independent, the direct relation being due to coincidental but constant occurrence of more frequent and severe complications in the older age groups. Both age and complicating diseases must be considered in estimating severity of coma. Therefore, one finds four “primary” fundamental factors influencing mortality, namely, (1) age, (2) diastolic blood pressure, (3) degree of unconsciousness and (4) complicating diseases. Figure 2*A* shows the relation of these four basis variables to mortality. It is seen that they all lie along the average “ideal” severity index sought and that the mean of these four curves will approach this “ideal” closely.

The curve of mortality versus age is closely approximated by a direct proportion:

$$(a) \text{ mortality} = \text{age}$$

The curve of mortality versus diastolic blood pressure is approximated by:

$$(b) \text{ mortality} = 100 \text{ diastolic blood pressure}$$

The curve of mortality versus degree of unconsciousness is approximated by:

$$(c) \text{ mortality} = 30 (\text{degree of unconsciousness}) - 25$$

in which the degree of unconsciousness is graded from 1 to 4.

The curve of mortality versus complicating diseases has been similarly approximated to simplify the final formula:

$$(d) \text{ mortality} = 30 (\text{severity of complication}) - 25$$

in which the severity of the complication is graded from 1 to 5.

Adding formulas (a), (b), (c) and (d) and dividing by 4 to obtain an average composition formula representing all these factors, one obtains:

$$\text{Mort. \%} = \frac{30 (\text{Uncon.}) - 25 + 30 (\text{Comp.}) - 25 + \text{Age} + 100 - \text{D.B.P.}}{4}$$

By simplifying one obtains:

$$\text{Mort. \%} = \frac{30 (\text{Uncon.} + \text{Comp.}) + \text{Age} + 50 - \text{D.B.P.}}{4}$$

in which

Mort. \% = predicted average percentage mortality

Uncon. = degree of unconsciousness (graded 1 to 4)

Comp. = severity of complication (graded 1 to 5)

Age = age of patient (years)

D.B.P. = diastolic blood pressure (mm. mercury)

By the use of this formula, one obtains a direct value in percentage which is equivalent to the average percentage mortality which a patient has according to this series of statistics.

For example, a 30 year old patient admitted semiconscious (grade 2), with a diastolic blood pressure of 60 mm. of mercury and no complicating diseases, has a prospective mortality of:

$$\text{Mort. \%} = \frac{30 (2 + 0) + 30 + 50 - 60}{4} = 20\%$$

From simple examination of this patient and use of this formula it is quickly determined that the prospective mortality of this patient is 20 per cent; i. e., he has one out of five chances of dying of coma.

Again for example, a 60 year old patient is admitted completely unconscious (grade 4), with no blood pressure obtainable and with gangrene of one foot and lobar pneumonia (grade 5 complication). The prospective mortality of this patient is:

$$\text{Mort. \%} = \frac{30 (4 + 5) + 60 + 50 - 0}{4} = 95\%$$

To indicate the accuracy of this formula, it was applied in the same 107 cases listed in table 17 and actual mortality was compared

to predicted mortality. For comparison of the formula with the severity indexes the cases were separated into five groups of 20 per cent each, groups which are actually too large to indicate the true accuracy of the formula. In figure 3 the actual mortality is plotted against predicted mortality by use of the formula; along the ordinate is plotted the actual mortality, and along the lower abscissa is plotted the mortality calculated by the severity formula for the same 107 cases. It is apparent that the formula as an index is superior to the Rabinowitch index and even closer to the "ideal" than the modified index. The fact that the actual mortality is slightly higher than the calculated mortality in the most severe coma is an advantage rather than a disadvantage, since improved methods of treatment will tend to lower the actual mortality and the actual and the calculated mortality will approach one another.

The formula indicates that although chemical values of the blood are indispensable in following the treatment of coma and in indicating the severity of acidosis, they are not necessary in estimating mortality in diabetic coma. Other writers<sup>8</sup> are in agreement that a much more accurate prognosis can be given from clinical data than from laboratory data.

The formula is recommended as being most valuable because (*a*) it is simplest, (*b*) it indicates percentage mortality directly without referring to a table or graph, (*c*) it is more accurate than either severity index and (*d*) it permits estimation of the severity of diabetic coma by simple examination without waiting for reports of chemical study of the blood.

#### SUMMARY AND CONCLUSIONS

A study of the various factors influencing the mortality in 315 cases of diabetic coma at the Los Angeles County General Hospital brings out the following:

1. Mortality statistics in diabetic coma are of no value unless attacks of coma of equal severity are compared.
2. Coma occurs more frequently during the puberal and the climacteric decade. Mortality is equal in the two sexes.
3. In the great majority of cases death in diabetic coma is due to shock or associated complicating disease. One half of all fatalities in coma occur between six and twenty-four hours after admission to the hospital.
4. Factors of greatest importance and of fundamental nature influencing the mortality of diabetic coma are (*a*) the age of the patient, (*b*) the diastolic blood pressure, (*c*) the degree of unconsciousness and (*d*) complicating diseases.

8. Dillon and Dyer.<sup>1c</sup> Wilder.<sup>5a</sup>

5. Factors of lesser importance in estimating severity of diabetic coma are (*a*) duration of coma, (*b*) blood nonprotein nitrogen and (*c*) blood sugar.

6. There is no relation between the carbon dioxide-combining power of the blood and mortality.

7. A modified index of severity is recommended for use in estimating severity of diabetic coma.

8. A severity formula is also derived which indicates severity of coma and allows one to predict average prospective mortality.

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# INTERRELATION OF THE FACTORS INFLUENCING MORTALITY IN DIABETIC COMA

## A STATISTICAL STUDY

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A study<sup>1</sup> of the various factors influencing the mortality of diabetic coma in 315 consecutive cases at the Los Angeles County General Hospital from 1930 through 1940 brought out the following conclusions:

1. Factors of greatest importance in influencing the mortality of diabetic coma are (*a*) the age of the patient, (*b*) the level of diastolic blood pressure, (*c*) the degree of unconsciousness of the patient and (*d*) the severity of the complicating disease.

2. Factors of lesser importance in estimating severity of diabetic coma are (*a*) the duration of coma before treatment is instituted, (*b*) the level of blood nonprotein nitrogen and (*c*) the level of blood sugar.

3. There is no relation between the carbon dioxide-combining power of the blood and mortality.

The previous study suggested that perhaps some of these factors are "primary," whereas others are "secondary," produced by and dependent on fundamental changes in the primary factors. For example, may it be assumed that elevation of blood nonprotein nitrogen is a secondary factor depending on age and blood pressure? Does severity of shock, acidosis, hyperglycemia or azotemia increase the longer the patient is in coma? Is the height of blood sugar dependent on the value of the carbon dioxide-combining power of the blood or vice versa? In an attempt to answer these and other similar questions cross analysis of the various factors was undertaken.

Theoretically, in a study of the relation of two interdependent variables, all other factors should be kept constant. For example, to study the relation of blood nonprotein nitrogen to age, a group of cases of uncomplicated coma should be selected in which there are the same degree of unconsciousness, height of blood pressure, level of blood sugar and carbon dioxide-combining power, etc., so that the only known

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Dr. Solomon Strouse contributed assistance, criticism and suggestions during the preparation of this paper.

1. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med., this issue, p. 347.

variables would be age and nonprotein nitrogen. This was attempted, and it was soon discovered that too few cases fell into each restricted group to warrant any deduction. Therefore, two variables were plotted against one another, on the assumption that the other factors would tend to balance out.

#### METHOD OF ANALYSIS

Figure 1 exemplifies the method used to study the interrelation of two factors. In this graph the cross analysis of the relation between blood sugar and the carbon dioxide-combining power of the blood is attempted. It is noted that of

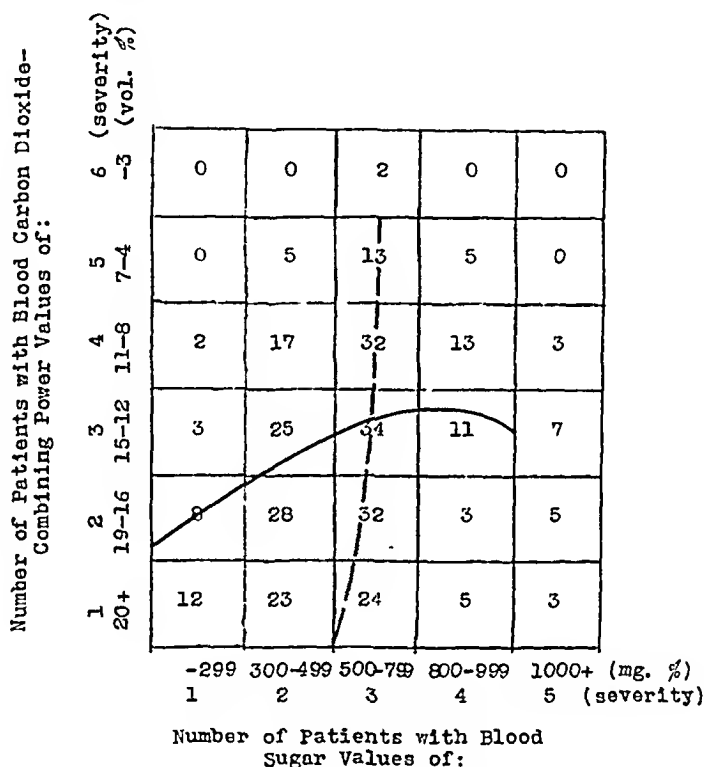


Fig. 1.—Interrelation of blood sugar and the carbon dioxide-combining power of the blood.

25 patients with blood sugar values of 299 mg. per hundred cubic centimeters or lower (severity of grade 1), 12 patients had a carbon dioxide-combining power of 20 volumes per cent or over (severity of grade 1), 8 had values of 19 to 16 volumes per cent (severity of grade 2), 3 had values of 15 to 12 volumes per cent (severity of grade 3) and 2 had values of 11 to 8 volumes per cent (severity of grade 4), with an average carbon dioxide-combining power for the whole group of about 19 volumes per cent. Similarly, patients with blood sugar values from 300 up to and including 499 mg. per hundred cubic centimeters (severity of grade 2) had carbon dioxide-combining power graded as follows: severity of grade 1, 23 patients; grade 2, 28 patients; grade 3, 25 patients; grade 4, 17 patients, and grade 5, 5 patients, with an average carbon dioxide-combining power for the group of about 16 volumes per cent. In like manner, it is determined that patients with blood sugar values from 500 to 799 mg. per hundred cubic centimeters (severity of grade 3) had an average carbon dioxide-

combining power of about 5 volumes per cent, patients with blood sugar values of 800 to 999 mg. per hundred cubic centimeters (severity of grade 4) had an average carbon dioxide-combining power of 12 volumes per cent and patients with blood sugar values of 1,000 mg. per hundred cubic centimeters or over (severity of grade 5) had an average carbon dioxide-combining power of about 15 volumes per cent. These average carbon dioxide-combining powers lie along the heavy solid line (fig. 1), which therefore indicates the relation between carbon dioxide-combining power of the blood and blood sugar, with blood sugar used as the independent factor and carbon dioxide-combining power as the dependent factor. In other words, it indicates whether and how carbon dioxide-combining power varies with blood sugar. It is evident that carbon dioxide-combining power definitely falls as blood sugar rises.

By using the same figure 1 and laying it on its side, the study may be repeated, with the carbon dioxide-combining power of the blood as the independent factor and blood sugar as the dependent factor. It is seen that of patients with a carbon dioxide-combining power of 20 volumes per cent or over (severity of grade 1), 12 patients had blood sugar values of .299 mg. per hundred cubic centimeters or under, 23 patients had values from 300 to 499 mg., 24 patients had values from 500 to 799 mg., 5 patients had values of 800 to 999 mg. and 3 patients had values of 1,000 mg. or over, with an average blood sugar value for the group of about 450 mg. per hundred cubic centimeters. Likewise, for each severity grade of carbon dioxide-combining power, the average blood sugar value is determined, and a second curve is obtained (fig. 1), indicated by the vertical broken line, which shows the variation of blood sugar with the carbon dioxide-combining power of the blood. It is evident that as the carbon dioxide-combining power falls, sugar on the average slightly rises.

It must be appreciated that the two curves obtained from the graph were calculated from the use of two separate sets of figures, even though these figures were all included within the same graph; the curve showing the dependency of the carbon dioxide-combining power of the blood on blood sugar was obtained by taking averages in a vertical direction, whereas the second curve, showing the dependency of blood sugar on carbon dioxide-combining power, was taken by averaging a different set of numbers in a horizontal direction.

In a similar manner through the use of thirty-two comparable graphs (too extensive to reproduce here), sixty-four curves were obtained, showing the interrelation of eight variables. These curves are aggregated and plotted to scale on one graph (fig. 2) for convenience and comparison.

Figure 2 shows the interrelation, through cross analysis, of the various factors influencing the severity and mortality of diabetic coma. Each factor is analyzed as though it were an independent fundamental factor, with all the other factors secondary. The factors are plotted according to their severity; namely, 0, normal level or absence of the factor; 1, the mildest degree, and 5, the most severe degree.

## RESULTS

*Age.*—In studying the dependency of the factors on the age of the patients, figure 2*a* has the abscissa (base line) divided into five groups, group 1 (15 years and under), group 2 (16 to 30 years), group 3 (31 to 50 years), group 4 (51 to 70 years) and group 5 (71 years and over). The following observations may be noted:

1. Average blood pressures, systolic and diastolic, in all age groups are about the same; patients in the older age groups do not tend to go



into shock more easily than children. However, in this series of cases it was rare for a patient over 45 years of age to go into shock and recover, whereas younger persons were admitted completely unconscious with blood pressures of zero and recovered.

2. The duration of coma is equal in all age groups. Children are not brought into the hospital earlier than adults.

3. The average values for blood sugar and blood nonprotein nitrogen are somewhat higher in the older age groups. These may be minor contributing factors to the higher mortality of aged patients, since it has been shown<sup>1</sup> that mortality is directly proportional to blood nonprotein nitrogen and somewhat dependent on blood sugar.

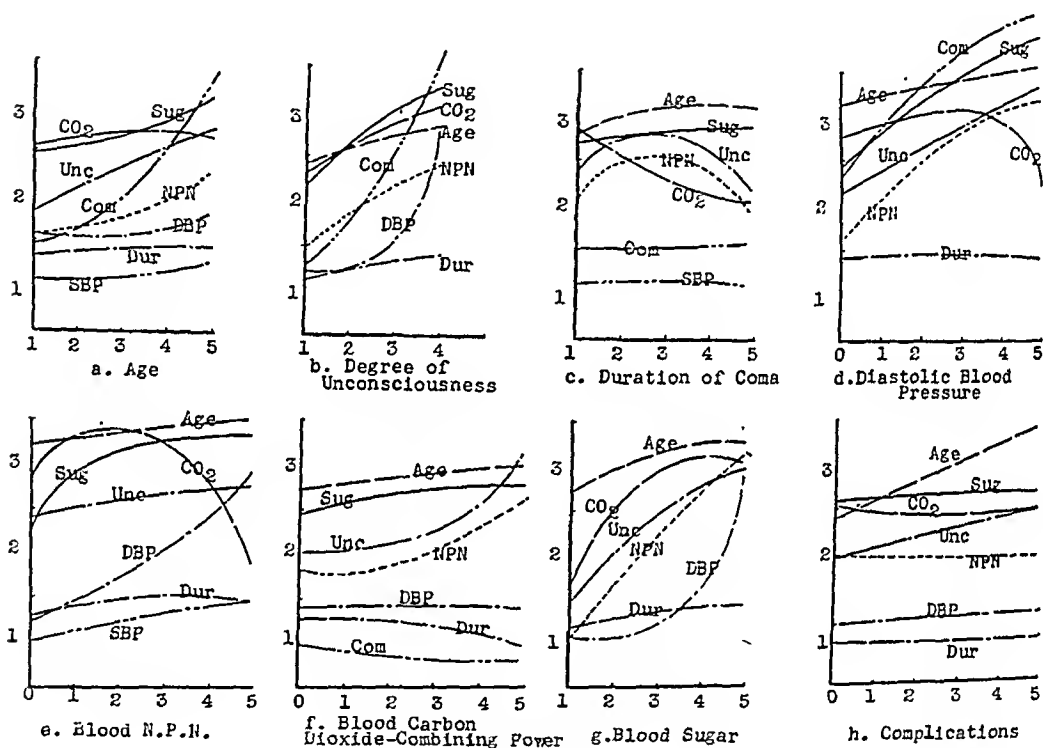


Fig. 2.—Interrelation of various factors influencing the severity of diabetic coma. The following abbreviations have been employed: *Sug*, blood sugar; *CO<sub>2</sub>*, carbon dioxide-combining power of the blood; *NPN*, nonprotein nitrogen content of the blood; *Unc*, degree of unconsciousness; *Com*, severity of complications; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure, and *Dur*, duration of coma.

4. The carbon dioxide-combining power of the blood has no relation to age. Aged patients do not go into acidosis more easily than children, or vice versa.

5. Patients in the older age groups have, on the average, a more severe degree of unconsciousness on admission. This may indicate that in "coma" they become unconscious more easily than do children, and may also be a contributing factor toward the increased mortality of the aged patients.

6. It is at once evident that the severity of complications is probably the most important single factor explaining the increased mortality of the older age groups. Figure 2a shows that complications in patients below 50 years of age are of mild severity. Complications are moderately frequent in children, being mostly acute infections of the upper respiratory tract with or without complicating otitis media, etc., with low mortality. In the older age group the majority of comas in this series of cases were complicated, and the majority of complications were pneumonia, heart disease and gangrene of the feet with sepsis, all severe complications usually warranting a severity grade of 4 or 5. Complications are not only more severe in older age groups but are more frequent. In this series, of those cases in which the patients were under 15 years of age, 40 per cent of the comas were complicated; of patients from 31 to 50 years, 53 per cent had complications, and of those patients over 70 years of age, 71.5 per cent had complications.

In summary, the age of the patient influences many factors; as age increases, severity and frequency of complications markedly increase, degree of unconsciousness definitely increases and average values for blood sugar and blood nonprotein nitrogen increase.

*Degree of Unconsciousness.*—Figure 2b shows the dependency of the various factors on the degree of unconsciousness. The base line is calibrated as 1 (drowsy), 2 (semiconscious), 3 (unconscious but responding to painful stimuli) and 4 (completely unconscious). Studying these curves, one finds the following statements can be made:

1. Although figure 2a shows that the degree of unconsciousness is dependent on age, the converse is not as marked. In other words, although elderly patients tend to have, on the average, a more marked degree of unconsciousness, unconscious patients are found to have an average age only moderately higher than that of drowsy patients. A 60 year old patient in coma has a 50 per cent chance of being unconscious (group 3) and only a 20 per cent chance of being drowsy. A patient admitted unconscious in diabetic coma has a 35 per cent chance of being 60 years old and a 20 per cent chance of being 25 years of age.

2. Duration of coma is practically independent of degree of unconsciousness. Unconscious patients on the average have been in coma only slightly longer than drowsy patients.

3. Blood pressure definitely varies with the degree of unconsciousness. As the degree of unconsciousness becomes more severe, the diastolic blood pressure rapidly falls. The majority of completely unconscious patients are in severe shock.

4. Rising values for blood sugar and blood nonprotein nitrogen and a falling value for the carbon dioxide-combining power of the blood all increase in severity with increasing depth of unconsciousness. Blood sugar and blood nonprotein nitrogen increase definitely, completely

unconscious patients having on the average one severity grade higher than drowsy patients. Although the severity of acidosis increases with the degree of unconsciousness, the changes are not as striking. The degree of acidosis increases (the carbon dioxide-combining power of the blood falls) only one-half a severity degree from drowsiness to complete unconsciousness.

5. Again, it is noted that the severity of complications is the most important factor of all. Patients admitted unconscious or completely unconscious usually have complications, the complicating disease usually being severe. In this series, if one considers only cases of complication in which the patient was unconscious (grade 3), the average severity of the complication was grade 4. It becomes apparent that the degree of unconsciousness of the patient influences all factors. It is a good indication of the severity of the complication and the degree of shock and is closely linked with age and with chemical changes in the blood.

*Duration of Coma.*—Figure 2c indicates the influence of the duration of coma on the various factors. The duration of coma is divided into five groups, 1 (twelve hours and under), 2 (thirteen to twenty-four hours), 3 (twenty-five to thirty-six hours), 4 (thirty-seven to forty-eight hours) and 5 (forty-nine hours and over).

1. It is interesting to note that the carbon dioxide-combining power of the blood definitely rises with duration of coma. It has also been demonstrated<sup>1</sup> that as duration of coma increases, mortality first rises, then falls; as the value of carbon dioxide-combining power falls, mortality first tends to fall, then later rises. Figure 2f also indicates the inverse relation between carbon dioxide-combining power and duration of coma; the lower values of carbon dioxide-combining power are usually associated with comas of short duration; the higher values of carbon dioxide-combining power, on the average, are present in patients who have been in coma over a longer period.

2. As duration of coma increases, the average degree of unconsciousness and the level of blood nonprotein nitrogen rise, to reach a peak at about thirty-six hours; then the severity of these factors decreases as time goes on.

The graphs indicate that after a patient has been in coma thirty-six to forty-eight hours, the average degree of unconsciousness, the level of blood nonprotein nitrogen and the percentage of mortality fall. It is suggested that untreated patients in coma and still alive after forty-eight hours survive because they can better tolerate acidosis.

*Blood Pressure.*—Figure 2d indicates the important influence of diastolic blood pressure on the various factors. Diastolic blood pressure is plotted along the abscissa in six groups, group 0 (over 70 mm. mercury), group 1 (69 to 60 mm. mercury), group 2 (59 to 50 mm. mercury), group 3 (49 to 40 mm. mercury), group 4 (39 to 30 mm. mercury) and group 5 (29 mm. mercury and under).

1. It is evident that all the important factors, namely, degree of unconsciousness, severity of complications, blood sugar and blood nonprotein nitrogen, rapidly increase in severity as blood pressure falls and depth of shock increases. This merely stresses the importance of blood pressure as a fundamental factor influencing the severity of coma.

2. Average age and duration of coma are not influenced by blood pressure to any significant degree. Shock is not more frequently present in aged patients than in young ones.

3. Peculiarly enough, the value of the carbon dioxide-combining power of the blood is usually relatively high in the most severe cases of shock; the lowest blood pressures tend to be accompanied by the highest values for carbon dioxide-combining power. It is shown in figure 2*f* that blood pressure is not dependent on the carbon dioxide-combining power.

*Blood Nonprotein Nitrogen.*—In figure 2*e* blood nonprotein nitrogen is plotted along the abscissa in six groups, group 0 (values below 40 mg. per hundred cubic centimeters), group 1 (41 to 60 mg.), group 2 (61 to 80 mg.), group 3 (81 to 100 mg.), group 4 (101 to 120 mg.) and group 5 (121 mg. and over).

1. Outstanding in figure 2*e* is the finding that diastolic blood pressure is definitely influenced by the degree of azotemia and that systolic blood pressure is affected to a lesser degree. Comparing figures 2*d* and *e*, one sees that blood nonprotein nitrogen varies with the diastolic blood pressure, just about the same as blood pressure varies with blood nonprotein nitrogen; there is a direct linear relation between the two.

2. Blood sugar increases with rising blood nonprotein nitrogen in the lower degrees of azotemia. After blood nonprotein nitrogen reaches about 80 mg. per hundred cubic centimeters, there is no further rise in average blood sugar values.

3. The carbon dioxide-combining power of the blood shows a remarkable relation to blood nonprotein nitrogen. The average level of carbon dioxide-combining power falls in lower degrees of azotemia, but in those cases in which uremia is definitely marked the carbon dioxide-combining power of the blood tends to be relatively high. Of 8 patients with values for blood nonprotein nitrogen over 100 mg. per hundred cubic centimeters, 3 patients had values for carbon dioxide-combining power of over 20 volumes per cent; the lowest value for this factor in this group was 8.9 per cent.

4. The degree of unconsciousness, age and duration of coma are not remarkably influenced by blood nonprotein nitrogen.

5. If one considers all cases, high values for blood nonprotein nitrogen are found just as frequently in uncomplicated, as in complicated, comas (not graphed). With the exception of uremia due to

primary nephritis with associated diabetic coma, there is no relation between average levels of blood nonprotein nitrogen and severity of complications.

*Carbon Dioxide-Combining Power of the Blood.*—Figure 2f indicates the influence of the carbon dioxide-combining power of the blood on the various factors. The carbon dioxide-combining power is plotted along the abscissa in six groups, group 0 (20 volumes per cent or over), group 1 (19 to 16 volumes per cent), group 2 (15 to 12 volumes per cent), group 3 (11 to 8 volumes per cent), group 4 (7 to 4 volumes per cent) and group 5 (3 volumes per cent or lower).

1. As the carbon dioxide-combining power of the blood falls, the degree of unconsciousness increases.

2. The blood nonprotein nitrogen rises moderately as the carbon dioxide-combining power falls. Since it has been demonstrated that diabetic acidosis produces renal tubular damage,<sup>2</sup> the deduction that increasing severity of acidosis would produce increasing azotemia is supported.

3. As discussed with reference to figure 2c, an inverse relation appears to exist between duration of coma and level of carbon dioxide-combining power. Figure 2f indicates that the lower values for carbon dioxide-combining power tend to be associated with comas of shorter duration.

4. Blood sugar is influenced only slightly by the carbon dioxide-combining power; a low value for the latter factor tends to be associated with slightly higher blood sugar levels than does a high value.

5. Age, blood pressure and severity of complications are not influenced to any remarkable degree by the level of the carbon dioxide-combining power. On the whole, figure 2f is notable by the absence of any influence of the carbon dioxide-combining power on the majority of severity factors, which again tends to minimize the importance of this factor in evaluating the severity of a diabetic coma.<sup>3</sup>

*Blood Sugar.*—Figure 2g shows the influence of blood sugar on the various factors. Blood sugar is plotted along the abscissa in five groups, group 1 (299 mg. per hundred cubic centimeters and under), group 2 (300 to 499 mg.), group 3 (500 to 799 mg.), group 4 (800 to 999 mg.) and group 5 (1,000 mg. and over).

The following observations may be made:

1. Blood nonprotein nitrogen definitely increases with rising blood sugar. Figures 2e and g reveal that a close relation exists

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2. Tollman, J. P., and Kirk, E. J.: Diabetes Mellitus with Reference to Kidney Pathology, *Am. J. Clin. Path.* 6:357-370, 1936.

3. Rabinowitch, J. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma, *Ann. Int. Med.* 12:1403-1428, 1939. Collen.<sup>1</sup>

between the two factors, a rise in one tending to be associated with a rise in the other; however, statistically, blood nonprotein nitrogen appears to be more dependent on blood sugar than vice versa.

2. The degree of unconsciousness varies with the level of blood sugar. With blood sugar values over 800 mg. per hundred cubic centimeters patients are usually unconscious, while with values under 500 mg. patients are usually semiconscious to drowsy.

3. Diastolic blood pressure definitely varies with blood sugar values, especially in cases of marked hyperglycemia. As blood sugar levels rise over 800 mg. per hundred cubic centimeters, blood pressure rapidly falls.

4. Average age, duration of coma and severity of complications (not shown on the graph) show slight increase with rising blood sugar levels.

5. Blood sugar is an important factor definitely influencing many of the variables which determine the severity of diabetic coma.

*Complicating Diseases.*—In figure 2*h* an attempt is made to study the influence of the presence of complications on the various factors. The complications are graded according to estimated severity from 1 (very mild) to 5 (very severe) and are plotted along the abscissa. The first group (0) comprises cases in which complications are not present.

1. Again the relation between age and complicating conditions is outstanding. It is evident that the more severe grades of complicating diseases are present in the older age groups.

2. It is also noted that the degree of unconsciousness rises with increasing severity of complication; however, this is not pronounced.

3. Blood sugar, blood nonprotein nitrogen and the carbon dioxide-combining power of the blood are not influenced by complicating diseases, indicating that the primary metabolic disturbances of diabetic coma are not essentially altered by a complication.

4. Blood pressure and duration of coma are not influenced by absence or presence of complications.

#### SUMMARY OF CROSS ANALYSIS OF FACTORS

A study of 315 cases of diabetic coma at the Los Angeles County General Hospital has brought out several factors which influence the mortality of diabetic coma. Cross analysis of the interrelation of these factors reveals:

1. The increasing mortality with age is primarily due to the increased number and the increased severity of complications in older age groups.

2. The degree of unconsciousness of a patient in diabetic coma varies with blood pressure, blood sugar, the carbon dioxide-combining

power of the blood, age and severity of the complicating disease in decreasing importance. The high mortality in severe degrees of unconsciousness is predominantly due to the presence of increased frequency and severity of complications and severe shock.

3. Duration of coma is of secondary importance; however, patients in diabetic coma who are untreated for over forty-eight hours and who are still alive form an interesting small group who seem to tolerate acidosis well and have only moderately severe coma.

4. The degree of shock varies with the degree of unconsciousness and the values for blood nonprotein nitrogen and blood sugar.

5. The degree of azotemia primarily varies with the blood sugar and the blood pressure and to a lesser extent with the degree of unconsciousness, age and the carbon dioxide-combining power of the blood in the order named. The high mortality in severe azotemia is probably due to associated shock, there being a direct relation between diastolic blood pressure and blood nonprotein nitrogen.

6. The carbon dioxide-combining power of the blood decreases with rising blood sugar and increasing depth of unconsciousness.

7. The degree of hyperglycemia is influenced by diastolic blood pressure and to a lesser extent by the degree of unconsciousness.

8. Although the presence of a complicating disease is an important factor influencing the mortality of a patient in coma, it does not appear to influence the level of blood sugar or blood nonprotein nitrogen or the carbon dioxide-combining power of the blood.

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# EXPERIMENTAL PRODUCTION OF EMPHYSEMA

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Emphysema is encountered in 2 to 5 per cent of all necropsies.<sup>1</sup> If we exclude the senile type of emphysema and those rare instances of emphysema due primarily to disease of the thorax, it may be said that it is a condition associated with bronchitis and bronchial spasm. These disorders obstruct respiration and bring about persistent pulmonary overdistention. Coughing, which always accompanies them, is thought to exaggerate this distention. Attacks of asthma are nearly always associated with pulmonary emphysema, and hay fever is becoming more important in any study of the disease.

Important in the emphysematous lung is the destruction of many capillaries in thin, atrophic alveolar walls, resulting in an obstructed pulmonary circulation.<sup>2</sup> This may lead to a high pulmonary arterial pressure with hypertrophy of the right side of the heart. Statistics compiled from autopsy material by various authors are not in agreement as to the incidence of this cardiac hypertrophy, but it is present in a varying percentage of cases.<sup>3</sup> The peripheral venous pressure is increased.<sup>4</sup> Vital capacity is reduced.<sup>5</sup> This is marked in cases of

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From the Department of Surgery, University of Chicago.

This work was done under a grant of the Douglas Smith Foundation, of the University of Chicago.

1. Christie, R. V.: Emphysema of the Lung, in Rolleston, H.: The British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 4, pp. 508-519.

2. Hamman, L.: Emphysema, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1940, vol. 2, pt. 1, pp. 68-81.

3. Alexander, H. L.; Luten, D., and Kountz, W. B.: The Effects on the Heart of Long-Standing Bronchial Asthma, J. A. M. A. **88**:882-884 (March 19) 1927. Kahn, M. H.: The Electrocardiogram in Bronchial Asthma, Am. J. M. Sc. **173**:555-562, 1927. Unger, L.: Heart in Bronchial Asthma, J. Allergy **2**:17-22, 1930. MacDonald, I. G.: The Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**:253-277, 1932. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:687-760 (Dec.) 1922. Crip, L. H.: Bronchial Asthma and Circulation, *ibid.* **49**:241-252 (Feb.) 1932.

4. Kountz, W. B.; Alexander, H. L., and Dowell, D.: Emphysema Simulating Cardiac Decompensation, J. A. M. A. **93**:1369-1371 (Nov. 2) 1929.

*(Footnotes continued on next page)*



severe emphysema, and there is an inability to cope with increased metabolic activities.

Efforts at active treatment of emphysema have been discouraging to say the least. Perhaps preventive therapeutics has more to offer. Thus more effort should be made to eliminate the cause, if that is possible.

#### THEORIES OF PATHOGENESIS

Several important types of emphysema have been recognized, namely, hypertrophic, or chronic obstructive, emphysema; atrophic, or senile, emphysema; acute vesicular emphysema associated with acute infections of the respiratory tract; localized, or compensatory, emphysema due to atelectasis or fibrosis, and surgical emphysema, or acute interstitial emphysema, associated with chest injuries or artificial pneumothorax.<sup>1</sup> Of this group probably the most important is hypertrophic, or chronic obstructive, emphysema.

Important factors to be considered in the production of emphysema are (1) increased pressure in the alveoli and (2) the resistance of the alveolar wall.<sup>2</sup> Of these, distention of the alveoli by increased pressure is usually thought to be the more important, especially in the obstructive type. Increased expiratory pressure with hyperpnea when inspiration is unobstructed leads to pulmonary distention. There is also a reflex increase in the force of inspiration. Coughing leads to an enormous increase in the expiratory pressure. It is the effects of combined inspiratory and expiratory pressures in the alveoli which cause the greatest degree of pulmonary distention and which if long maintained are believed to lead to true substantive emphysema. Emphysema is commonly encountered as a result of chronic bronchitis and asthma. In cases of chronic bronchitis the degree of obstruction to all parts of the lung varies because of edema, infection and the presence of tenacious secretions. The parts supplied by the most obstructed bronchi become distended, even though there is no hyperpnea. Normally the force of inspiration is greater than that of expiration. The elasticity of the lung and thorax is sufficient to deflate the unobstructed lung but not to deflate fully the obstructed parts. Increase in respiratory effort leads only to increased pulmonary distention. This eventually may lead to permanent dilatation of the alveoli.

*Changes in the Thorax.*—Freund<sup>6</sup> first described degenerative changes which lead to an increase in the size of the thorax. He men-

5. (a) Kountz, W. B., and Alexander, H. L.: Emphysema, *Medicine* **13**:251-316, 1934. (b) Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum, *Arch. Int. Med.* **64**:913-926 (Nov.) 1939. (c) Hamman.<sup>2</sup>

6. Freund, W. A.: Der Einfluss der primären Erkrankungen des knorpeligen Thorax auf Entstehung gewisser Lungenkrankheiten, *Verhandl. d. phys.-med. Gesellsch. in Würzburg* **9**:223, 1859.

tioned the lengthening and thickening of the costal cartilages and the ribs. Other authors expressed the belief that kyphosis of the thoracic portion of the spine was important in altering the size of the chest and as a cause of emphysema.<sup>7</sup> The atrophic changes of old age may be a factor in the production of emphysema. There is a tendency for the chest to become barrel-shaped, thus increasing the thoracic space and leading to so-called "senile emphysema."

*Heredity.*—Some authors have proposed that there is an inherited tendency to such conditions as chronic bronchitis and asthma which lead to emphysema. Further, they have suggested that developmental defects of the bony thorax may lead to emphysematous changes in the lungs.<sup>8</sup>

*Defects in the Lung and the Pleura.*—Such degenerative and developmental changes are more apt to be secondary than primary in the causation of emphysema.

*Occupational Factors.*—In glass blowing and wind instrument playing there is increased expiratory pressure. This leads to pulmonary distention which may become permanent, but not to emphysema. It would seem that emphysema does not develop in the absence of hyperpnea.<sup>9</sup>

#### PREVIOUS ATTEMPTS AT EXPERIMENTAL PRODUCTION OF EMPHYSEMA

According to Harris and Chillingworth,<sup>10</sup> the first attempts to produce emphysema were made by use of a plethysmograph which enclosed an animal's entire body in a negative pressure chamber. The trachea was connected with the outside atmospheric pressure, so that the intrapulmonary pressure was in excess of the extrathoracic pressure of the chamber. This method did not simulate natural conditions of the disease, so these workers devised a ball valve type of obstruction which was placed in the trachea of dogs. They made studies which varied from twenty-four hours to three weeks in duration. Pathologic changes characteristic of emphysema except for the production of fibrous tissue developed in their dogs. Prolonged, or chronic, experiments were not done, nor was the intrapulmonary pressure measured.

7. Loeschcke, H.: Aus Lungenemphysem, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 3, pt. 1, pp. 612-700.

8. Engelhard, A.: Lungenemphysem aus bronchialer Lungenbläkung, *Deutsches Arch. f. klin. Med.* **175**:38-49, 1933.

9. Kaltreider, N. L.: Pathological Physiology of Emphysema, *Internat. Clin.* **2**:83-111, 1936. Kountz and Alexander.<sup>5a</sup>

10. Harris, W. H., and Chillingworth, F. P.: The Experimental Production in Dogs of Emphysema with Associated Asthmatic Syndrome by Means of an Intratracheal Ball Valve, *J. Exper. Med.* **30**:75-85, 1919.

Friedman and Jackson<sup>11</sup> made studies of the carbon dioxide content of the blood and the alveolar air during obstructed expiration, such as occurs in asthma, and concluded that the increased intrabronchial pressure interferes with the free flow of blood through the pulmonary capillaries, resulting in venous stasis and accumulation of carbon dioxide in the blood. This, in turn, causes an increase in the carbon dioxide of the alveolar air. They produced emphysematous changes in animals by the use of a valve which was placed in the trachea. That is, the alveoli were dilated and ruptured, but production of fibrous tissue was not noted. Their experiments were of the acute type, lasting three to eight hours. The pressure in the carotid artery was also studied and observed to drop consistently even with a slight increase in the intrabronchial pressure.

Kountz, Alexander and Dowell<sup>4</sup> reported a large series of cases of advanced emphysema with its associated effect on the heart. Experimental studies on dogs, in which a ball valve had been used, showed that extensive emphysema could be produced in a few weeks. They concluded that advanced emphysema does not necessarily affect the heart and that peripheral venous pressure varies directly with changes in pressure in the pleural cavity.

Kountz, Pearson and Koenig<sup>12</sup> attempted to determine the point of obstruction to the venous return in instances of emphysema with increased intrapleural pressure. They concluded that although there may have been some obstruction to the normal blood flow through the lungs, the chief obstruction was at or peripheral to the entrance of blood into the thorax. Certainly the delay occurred before the blood reached the right side of the heart.

Hinshaw<sup>13</sup> made further attempts at production of emphysema by a modification of the original ball valve type of tracheal obstruction.

Paine,<sup>14</sup> studying the changes in elasticity and histologic structure of the lung, inserted special valves into the trachea in dogs to produce respiratory obstruction and used operative procedures tending to change the thorax in dogs. He concluded that emphysematous changes of the pulmonary parenchyma occur within four to thirty-four weeks when either inspiration or expiration is obstructed and that similar changes

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11. Friedman, E. D., and Jackson, H. C.: The Carbon Dioxide Content of Blood and of Alveolar Air in Obstructed Expiration, *Arch. Int. Med.* **19**:767-776 (May) 1917.

12. Kountz, W. B.; Pearson, E. F., and Koenig, K. F.: Observations on Intrapleural Pressure and Its Influence on Relative Circulation Rate in Emphysema, *J. Clin. Investigation* **11**:1281-1291, 1932.

13. Hinshaw, H. C.: Experimental Production of Chronic Obstructive Emphysema in Animals, *Proc. Staff Meet., Mayo Clin.* **13**:599-600, 1938.

14. Paine, J. R.: Experimental Production of Pulmonary Emphysema, *J. Thoracic Surg.* **10**:151-175, 1940.

occur within eighteen to twenty-five weeks if the anterior portion of the diaphragm is reefed.

In most of these experiments prolonged studies were not attempted.

Previous work on the effects of known positive pressure in intratracheal anesthesia was done in this department by Marcotte and associates.<sup>15</sup> Their work indicated certain dangers in increased intrabronchial pressure. They found that mediastinal emphysema, pneumothorax and laceration of the pulmonary tissues were produced by pressures as low as 18 mm. of mercury. The mechanism of this phenomenon has been well explained by Macklin.<sup>16</sup> Moreover, once mediastinal emphysema had occurred, it tended to continue, even though the pressure dropped below the level necessary to initiate it. It was also noted that intrabronchial pressure depends chiefly on the patency of the outlet rather than the pressure at which air is forced into the lungs.

#### EXPERIMENTAL PROCEDURE

In our present work we have attempted to carry out acute and chronic experiments testing the theory of the production of emphysema by elevated intrabronchial pressure. An attempt was made to simulate in dogs the short inspiration and the prolonged difficult expiration of a person with chronic asthma at the height of an attack. In a person with asthma expiration is accompanied by a relatively marked increase in intrabronchial pressure because of the obstructed air passages; whereas inspiration is not accompanied by any increase in intrabronchial pressure.

Intermittent overinflation of the lungs was carried out in biweekly fifteen minute periods with controlled intrabronchial pressure. Air was introduced under positive pressure into the trachea near the primary bifurcation (carina) and permitted to escape back through the upper part of the trachea and the mouth. This outlet was obstructed so that various pressures could be maintained within the bronchial tree. The period during which air was introduced was arbitrarily three times as long as the period during which the air escaped, in keeping with the longer expiratory period of an asthmatic person. This intermittent overinflation was carried out at a rate of approximately twenty-eight times per minute, or about the normal respiratory rate in dogs. Experiments with 2 dogs were carried on for eleven months.

Ten dogs were used (table 1). Three were used for acute study and 7 for chronic study. On 3 of the latter group acute studies were also made at the end of the period of chronic study. The acute experiments varied from thirty-five to seventy-seven minutes in duration; the chronic, from one week to eleven months. The number of inflations with intermittent positive pressure varied from one to seventy-six, and the intrabronchial pressures, from 20 to 50 mm. of mercury, 35 mm. of mercury being the usual pressure in the chronic experiments.

*Apparatus.*—This consisted of a modified windshield wiper which was attached to an air source. The wiper was so constructed that the pressure delivered and the length of the "on" cycle and rate per minute could be easily adjusted. Large

15. Marcotte, R. J.; Adams, W. E.; Phillips, F. J., and Livingstone, H.: Differential Intrabronchial Pressures and Mediastinal Emphysema, *J. Thoracic Surg.* 9:346-355, 1940.

16. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Local Over-Inflation of Lung Substance, *Canad. M. A. J.* 36:414-420, 1937.

# Summary of Results of Overinflation of Lungs of Ten Dogs with Intermittent Positive Pressure

Dog No.	Type of Experiment	Duration of Experiment	No. of Experiments	Physiologic Effects						Cause of Death	Pathologic Condition		
				Intra-bronchial Pressure, Mm. Hg			Average Pulse Rate, Beats per Min.				Gross Examination	Microscopic Examination	
				Initial	During	After	Initial	During	After				
1	884	Acute	77 min.	1	22	170	110	...	...	...	Acute experiment with pressure studies	Mediastinal emphysema; heart and lungs grossly normal	
2	157	Acute	47 min.	1	20	90	70	...	...	...	Acute experiment with pressure studies	Moderate mediastinal emphysema; heart and lungs grossly normal	Interstitial emphysema; slight dilatation of terminal respiratory units
3	182	Acute	42 min.	1	50	160	80	...	...	...	Acute experiment with pressure studies; probable failure of right side of heart	No mediastinal emphysema; heart and lungs apparently normal	Interstitial emphysema; slight dilatation of terminal respiratory units; also thickening of pleura with pigment-containing macrophages present subpleurally
4	682	Chronic	1 wk.	2	35	...	...	...	...	...	Mediastinal emphysema; air embolism	Mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
5	683	Chronic	1 wk.	2	35	...	...	...	...	...	Mediastinal emphysema; air embolism	Mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
6	711	Chronic	2½ wk.	4	35	146	...	104	163	155	Mediastinal emphysema; spontaneous pneumothorax	Spontaneous pneumothorax; mediastinal emphysema; air embolism; pulmonary hemorrhage	Interstitial emphysema; some dilatation of terminal respiratory units
7	496	Chronic	7 mo.	39	35	124	85	144	149	137	Mediastinal emphysema; spontaneous pneumothorax	Pneumothorax; mild mediastinal emphysema	Slight interstitial emphysema; dilatation of terminal respiratory units; unresolved pneumonia with pulmonary emphysema; respiratory pores enlarged and irregular
8	754	Chronic	7½ mo.	49	35	139	108	158	159	185	Acute experiment with pressure studies	See 11 below	
9	657	Chronic	8 mo.	47	35	124	96	141	184	199	Acute experiment with pressure studies	See 12 below	
10	341	Chronic	11 mo.	75	35	128	123	147	178	196	Acute experiment with pressure studies	See 13 below	Middle lobe of right lung removed after 2 mo.; some dilatation of terminal respiratory units; respiratory pores enlarged and irregular
11	754	Chronic and acute	48 min.	50	35	170	128	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of alveolar walls; respiratory pores enlarged and irregular
12	657	Chronic and acute	40 min.	48	35	120	70	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of alveolar walls; respiratory pores enlarged and irregular
13	341	Chronic and acute	35 min.	76	26	160	122	...	...	...	Acute experiment with pressure studies	No mediastinal emphysema; heart and lungs apparently normal	Less interstitial emphysema than in dogs 157 and 182; dilatation of terminal respiratory units with slight fragmentation of alveolar walls; respiratory pores enlarged and irregular

rubber tubing led from the wiper to the trachea. Within this tube was a smaller tube leading from a mercury manometer to the exit of air within the bronchial tree. This double tubing was led through a tight face mask and airway down to the carina. The mask had an adjustable air outlet for regulation of intratracheal pressure and escape of air (fig. 1).

*Technic and Method (Preparation of Dogs).—*The chronic experiments were carried out as follows: A dog was given an injection of 10 cc. of morphine and atropine solution ( $\frac{1}{4}$  grain [0.015 Gm.] of morphine sulfate and  $\frac{1}{150}$  grain [0.0004 Gm.] of atropine sulfate per cubic centimeter) twenty to thirty minutes before overinflation was done. When fully asleep the dog was placed on its back on the table. The direct femoral artery blood pressures were taken before, during and after the overinflation. By use of the mouth gag and under direct vision the air tube was introduced into the lower portion of the trachea and the face mask applied.

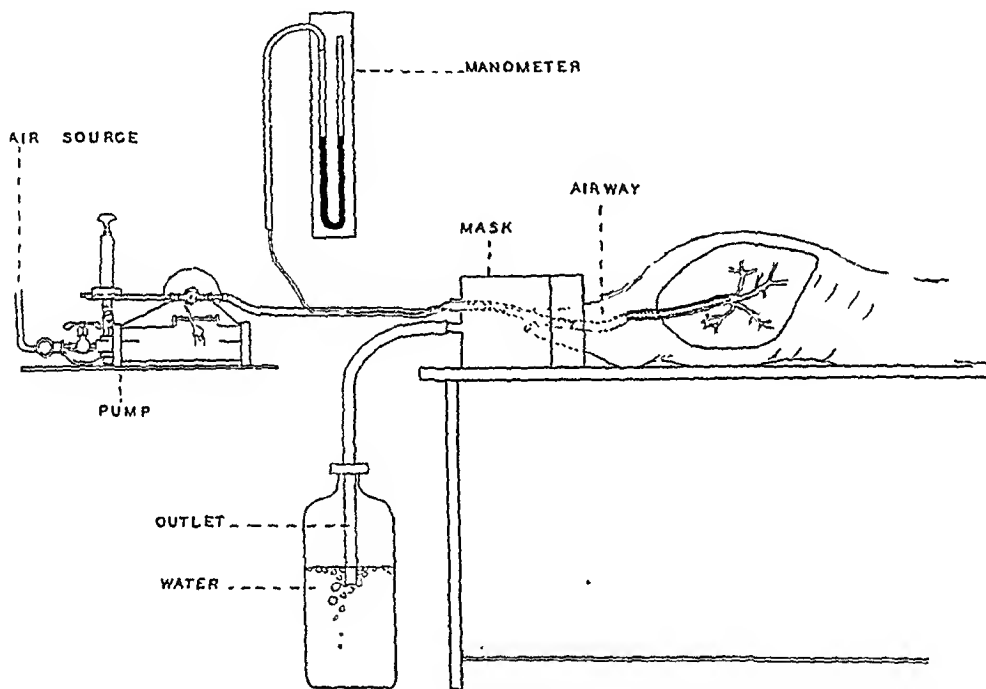


Fig. 1.—Apparatus for overinflation of lungs by intermittent positive pressure.

The air pressure was then turned on and maintained, as described earlier, for fifteen minutes at a maximum of 30 to 35 mm. of mercury at the level of the carina.

After several months of biweekly overinflation in 2 dogs used for chronic experiments (341 and 496) the middle lobe of the right lung was removed for gross and microscopic study and for comparison with the autopsy specimen.

Similar acute experiments were carried out. In these, kymographic tracings were made of the intratracheal air pressure, the pressure in the femoral artery and the pressure in the superior vena cava by means of a seeker introduced through the external jugular vein to a point several centimeters above the right auricle. These pressure studies were made continuously throughout the experiment and long enough afterward to permit observation of recovery phenomena. Pressures above 35 mm. of mercury were apt to cause serious overdilatation of the stomach. This was prevented by ligation of the esophagus before starting the experiment. In the chronic experiments air often escaped into the stomach and was evacuated by a stomach tube to permit resumption of normal respiration.

*Mortality and Health of Dogs.*—In several chronic experiments pressures up to 45 to 50 mm. of mercury were obtained by accident. Two of these dogs (682 and

683) died within a few minutes after the beginning of the experiment. Otherwise, there were no fatalities. Healthy, adult, mongrel dogs were used for the experiments. In several instances they actually gained weight in spite of the frequent doses of morphine and at least two foodless days a week. Morphine addiction, if present at all, was not severe.

*Preparation of Specimens.*—All autopsy specimens were prepared by removing the lungs from the animal and allowing Kaiserling I solution to gravitate into the trachea and air passages, thus displacing the air; the trachea was then clamped, and the lungs were immersed in the same fluid until thoroughly fixed. Sections were then cut for microscopic study. Special stains for connective and for fibrous tissue as well as the usual hematoxylin and eosin were used in this study.

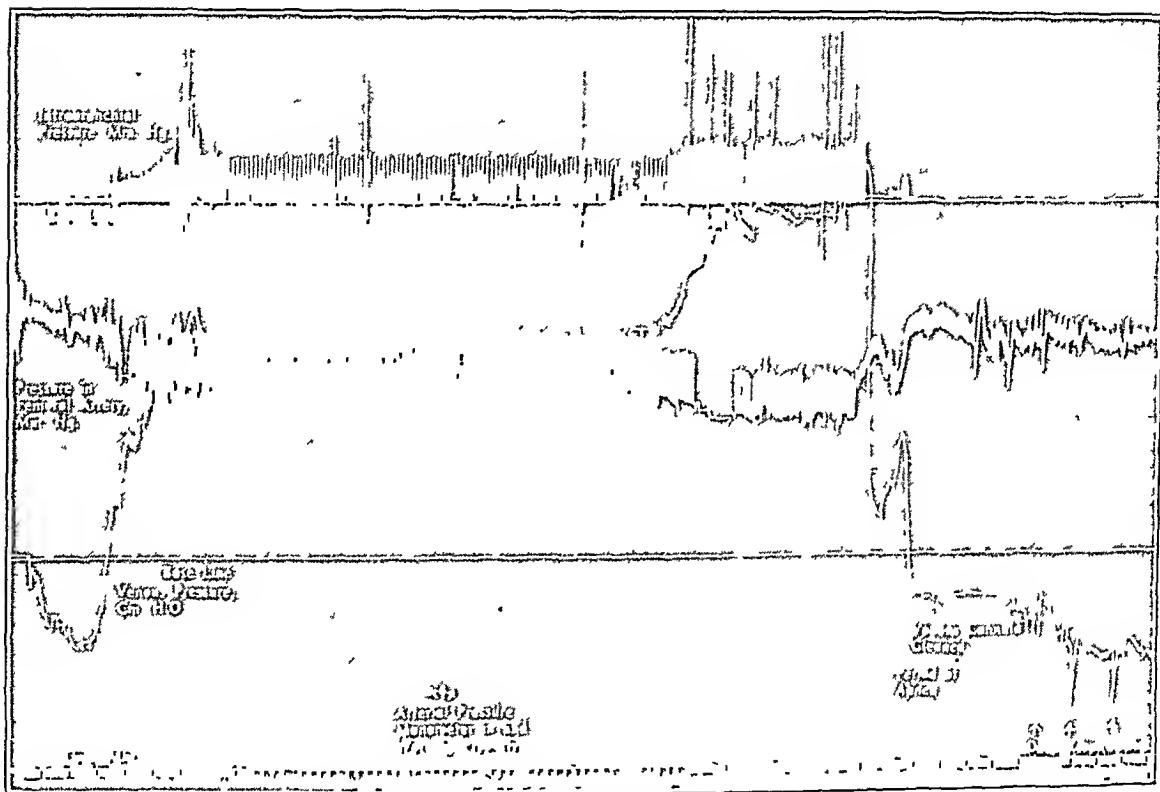


Fig. 2 (dog 341).—Kymogram made during overinflation of lungs by intermittent positive pressure showing the effects of increased intermittent intrabronchial pressure after eleven months of biweekly overinflation. The dog was quiet. The intrabronchial pressure is recorded in millimeters of mercury above; the systemic arterial pressure is recorded in millimeters of mercury in the center, and the venous pressure is recorded in centimeters of water below. The venous pressure rises directly with the intrabronchial pressure, whereas the systemic arterial pressure falls. An intrabronchial pressure of 30 mm. of mercury was maintained during the first ten minutes, and a pressure of 35 mm. of mercury, for six minutes. (Scale, 1:2.88.)

#### PROTOCOL

Dog 341.—A healthy collie weighing 10.37 Kg. was subjected to increased intrabronchial pressure first on July 9, 1939 and thereafter biweekly until June 8, 1940.

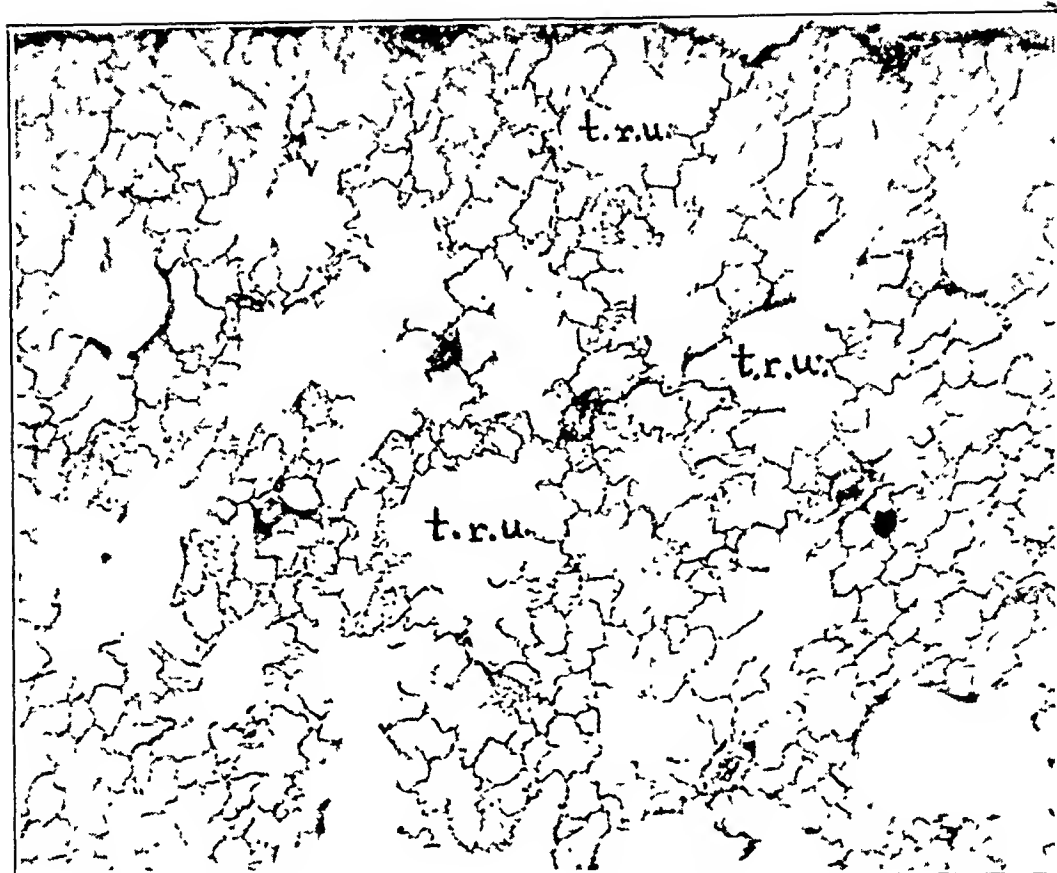


Fig. 3 (dog 341).—Parenchyma of lung at the periphery of a lobe, low magnification. There is moderate dilatation of the terminal respiratory units (*t.r.u.*), with occasional fragmentation of an alveolar wall. No true emphysematous changes are apparent.

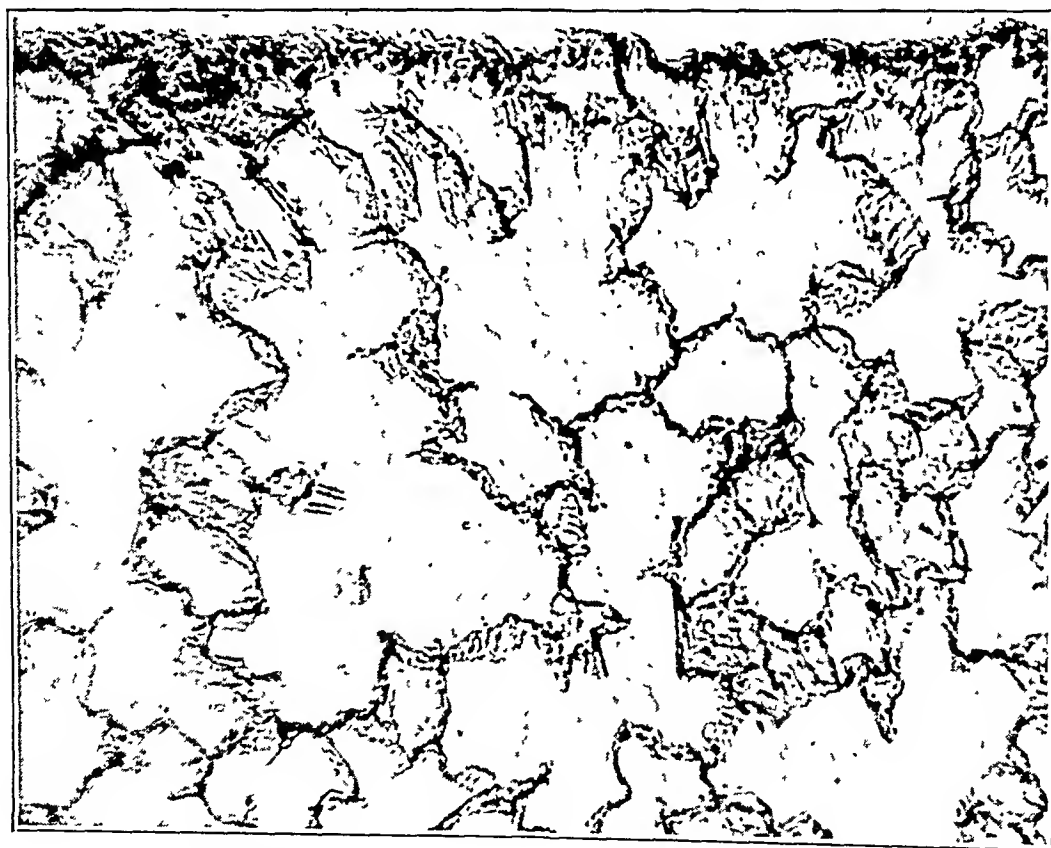


Fig. 4 (dog 341).—Parenchyma of the lung at the periphery of a lobe, high magnification.



On Sept. 11, 1939, after two months of biweekly inflation, the middle lobe of the right lung was removed for gross and microscopic study. Two and one-half weeks (eighteen days) later overinflation by increased pressure was resumed and continued until June 13, 1940, when the dog was killed. Its weight on this date was 10.75 Kg. The dog was given one and one-half times the usual dose of morphine and subjected to the routine fifteen minutes of increased pressure. During this period kymographic pressure studies were made, after which the dog was observed for another twenty minutes (fig. 2). The dog was then electrocuted.<sup>17</sup>

*Postmortem Observations.*—The trachea was clamped before the chest was opened, at which time the lungs were found fully expanded. Except for one small bandlike adhesion between the lower lobe of the right lung and the site of the lobectomy wound (the middle lobe had been removed) the pleural cavity was normal. There was no gross evidence of mediastinal emphysema. This was in contrast to the presence of mediastinal emphysema in all dogs on which only the acute type of experiment was performed. The heart and lungs appeared normal.

*Microscopic Study.*—Biopsy Specimen: There was a tendency to dilatation of the terminal respiratory units. The respiratory pores were somewhat larger than in normal lung tissue. There was no dissection or interstitial emphysema as such. When the lobe of the lung was cut across there was little tendency for the parenchyma to collapse. (The parenchyma of the lungs collapsed considerably only after acute experiments when they were cut across after fixation.)

*Autopsy Specimen:* There was more marked dilatation of the terminal respiratory units, e. g. the alveolar ducts and sacs, with slight tendency to fragmentation of the alveolar walls in some areas. There was slight perivascular and peribronchial interstitial emphysema. This was not as marked as that encountered after the acute experiments. There was no evidence of pulmonary emphysema as defined by destruction of the elastic or the fibrous tissue or of the capillaries of the alveolar walls (figs. 3 and 4).

*Comment.*—This protocol represents the technical procedures carried out both in the acute and in the chronic type of experiment. It does not represent the physiologic and pathologic findings in the acute type of experiment, as shown in the table.

#### RESULTS OF EXPERIMENTS

*Physiologic Effects of Intermittent Overinflation.*—Arterial blood pressures taken five minutes after the institution of positive pressure were an average of 38.3 mm. of mercury lower than the initial pressure, which varied from 90 to 170 mm. of mercury. A partial recovery then occurred during the period of inflation. Pressures taken five minutes after the inflation was discontinued were slightly higher than the initial level. There was a sharp rise to a high level of venous pressure as soon

17. Hrdina, L. S.: Electrocution in Sacrificing Laboratory Animals, *J. Lab. & Clin. Med.* **15**:86, 1929.

as inflation was begun. The rise varied directly with the intratracheal positive pressure.

*Pulse Rate.*—There was a tendency toward slight increase in the pulse rate after beginning the inflation, though this was by no means uniformly true. The rate after inflation approximated the initial rate.

*Cause of Death.*—The 3 acute dogs were electrocuted at the end of the pressure study. Three of the chronic dogs (754, 657 and 341) were likewise studied and killed. Two of the remaining 4 chronic dogs (682 and 683) died during the second inflation, with mediastinal emphysema and air embolism as causes of death. The other 2 chronic dogs died of mediastinal emphysema and spontaneous pneumothorax, 1 (711) after 4 inflations and the other (496) after 39 inflations.

*Gross Pathologic Effects.*—Two of the acute dogs showed a moderate amount of mediastinal emphysema with no apparent changes in the lungs or heart after inflation for seventy-seven and forty-seven minutes at pressures of 22 and 20 mm. of mercury, respectively, (intrabronchial). One dog (182) after forty-two minutes of inflation at an extreme pressure of 50 mm. of mercury did not show mediastinal emphysema or other apparent change in the lungs or heart.

In the group of 3 chronic dogs studied acutely from thirty-five to forty-eight minutes with intrabronchial pressures varying from 26 to 35 mm. of mercury no mediastinal emphysema or apparent change in the heart or lungs was encountered at autopsy.

Two of the 4 remaining chronic dogs died after the second inflation at an intrabronchial pressure of 35 mm. of mercury with mediastinal emphysema, air embolism and gross subpleural pulmonary hemorrhage.<sup>17a</sup> Another (711) died after the fourth inflation, showing a spontaneous pneumothorax, mediastinal emphysema, air embolism and subpleural hemorrhage. The other dog (496) in this group died of a large pneumothorax at the end of the thirty-ninth inflation at a pressure of 35 mm. of mercury. A slight degree of mediastinal emphysema was also present.

#### MICROSCOPIC STUDY

*Acute Experiments.*—The lungs and pleurae of 2 acute dogs (157 and 182) were studied microscopically. The terminal respiratory units, namely, the alveolar ducts and sacs, in some areas, showed slight dilatation. There were also separation and breakdown of the peribronchial and the perivascular tissue, with formation of slitlike air—

17a. Coughing, with temporary elevation of intrabronchial pressure to as high as 50 mm. of mercury was occasionally observed in these experiments.

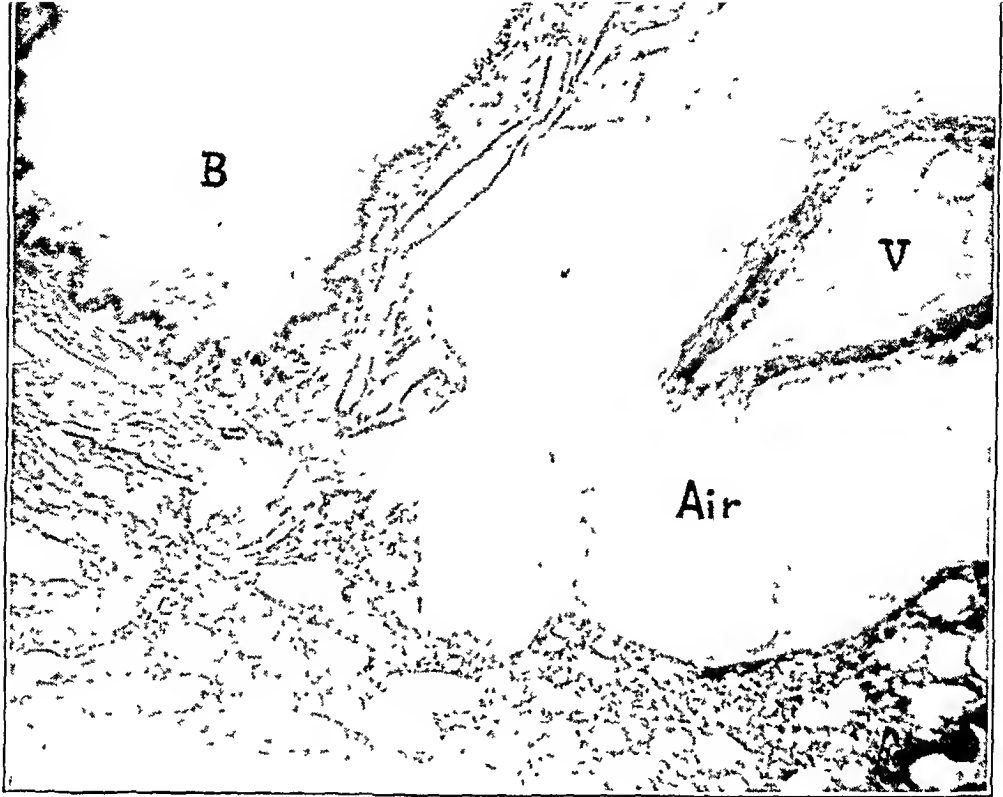


Fig. 5 (dog 683).—Section of lung made after the death of the animal from overinflation. Note the interstitial emphysema (*Air*) separating the bronchial wall (*B*) and the parenchyma from a vessel (*V*), with partial collapse of the last-named structure.

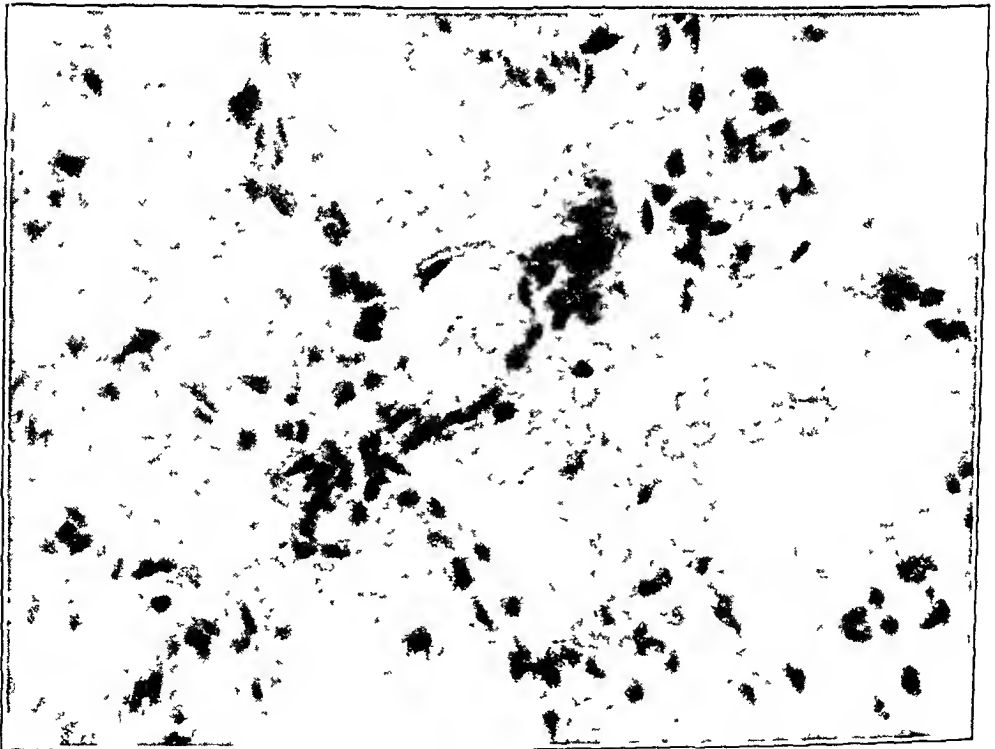


Fig. 6 (dog 683).—Section of lung made after death from overinflation. Note the hemorrhage into the alveoli. (This animal also had air embolism of the pulmonary veins and coronary arteries, besides mediastinal emphysema.)

containing spaces.<sup>5b</sup> The alveoli appeared to be normal, as did the rest of the lung tissue. Sections of lung from dog 182 showed many subpleural macrophages with old pigment. The pleura was much thicker than normal. The latter changes probably explain the failure of interstitial emphysema to develop in this dog.

*Chronic Experiments.*—Three of the 7 dogs in this group (682, 683 and 711) died during the early part of the experimental period. Microscopically, perivascular and peribronchial interstitial emphysema (fig. 5) was present in sections of the lungs of all 3 dogs. The terminal respiratory units showed changes similar to those seen in the dogs subjected to more acute experiments. However, some evidence of overdistention and rupture of the alveolar walls was present. There was rather marked pulmonary hemorrhage into many of the alveoli, and the perivascular and peribronchial emphysematous spaces (fig. 6). The latter finding was peculiar to these 3 dogs.

In dogs 341 and 496 the middle lobe of the right lung had been removed for microscopic study two and five months, respectively, after the beginning of the experiments. The microscopic sections do not represent the appearance of pulmonary tissue immediately after an overinflation. There was no evidence of perivascular and peribronchial interstitial emphysema. There was some tendency to dilatation of the terminal respiratory units. The alveoli appeared relatively normal except for the respiratory pores of the alveolar walls, which were somewhat larger than those in normal lung tissue.<sup>18</sup>

Three of these 4 chronic dogs (754, 657 and 341) were killed after an acute terminal experiment. Microscopic sections of the lungs of the 3 dogs showed similar changes, the most severe being encountered in dog 657. There was some perivascular and peribronchial interstitial emphysema. This was not as marked as that seen after the acute experiments on dogs 157 and 182. There was more marked dilatation of the terminal respiratory units, with a slight tendency to fragmentation of the alveolar walls in some areas. There was no evidence of pulmonary emphysema as defined by destruction of elastic and fibrous tissue and of the capillaries in the alveolar walls.

The chronic experiment was carried on for seven months (dog 496) and yielded the following microscopic data: On biopsy there was some dilatation of the peripheral air passages but no perivascular or peribronchial interstitial emphysema (fig. 7). These were similar to the

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18. Loosli, C. G.: Inter-alveolar Communications in Normal and in Pathologic Mammalian Lungs, Arch. Path. 24:743-776 (Dec.) 1937.

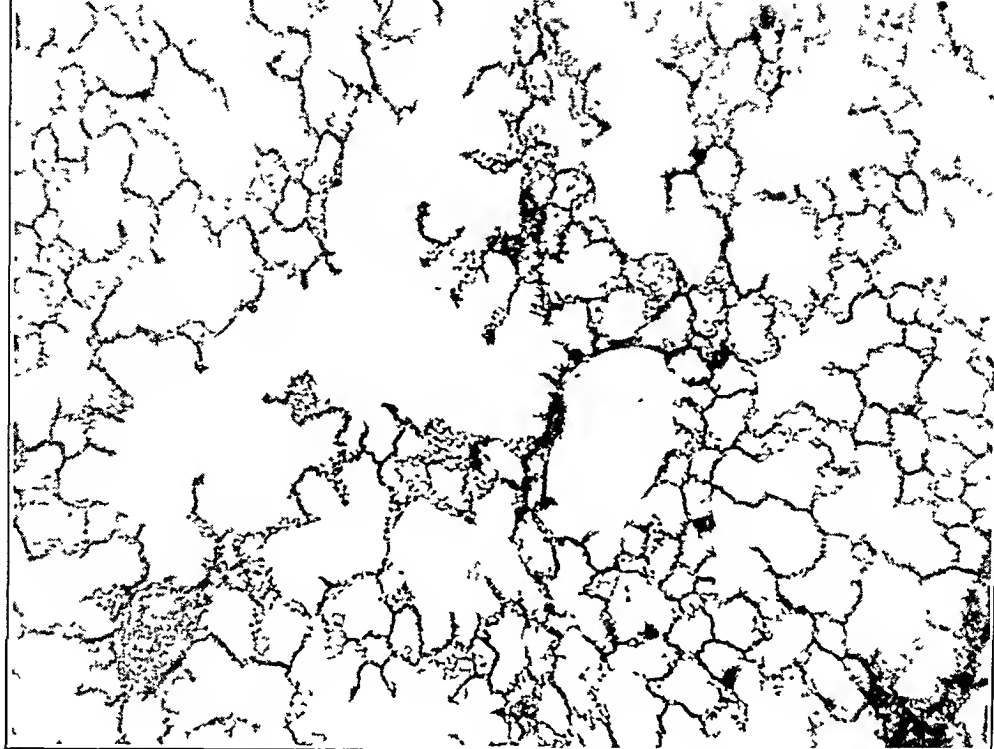


Fig. 7 (dog 496).—Repeated overinflation for seven months was accompanied by spontaneous infection of the lungs during the last two months. A microscopic section of the middle lobe of the right lung removed after five months shows slight dilatation of the terminal respiratory units with no emphysema.

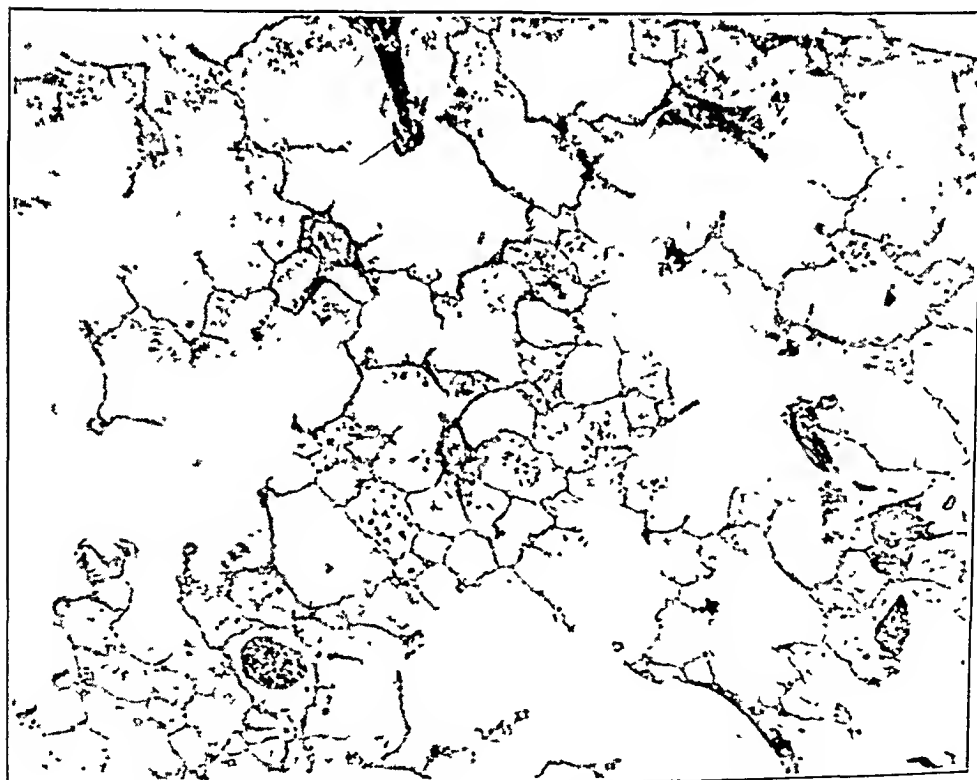


Fig. 8 (dog 496).—Section of the lung of the dog in figure 7 made after death of the animal from a pneumothorax occurring during overinflation. The magnification is the same as that in figure 7. Note the cellular infiltration and the definite emphysematous changes in the parenchyma of the lung.

changes encountered in the biopsy sections of the lung of dog 341. On autopsy the sections showed an old pneumonia. Many of the terminal respiratory units showed extreme dilatation with some destruction of capillaries and other elements of the walls (fig. 8). There were areas of fibrous tissue and unresolved pneumonia with large numbers of lymphocytes and polymorphs (fig. 9).

We believe we should not draw any conclusions from the sections made in this single experiment, since an infection was present and such was not the case in any other dog.<sup>19</sup>

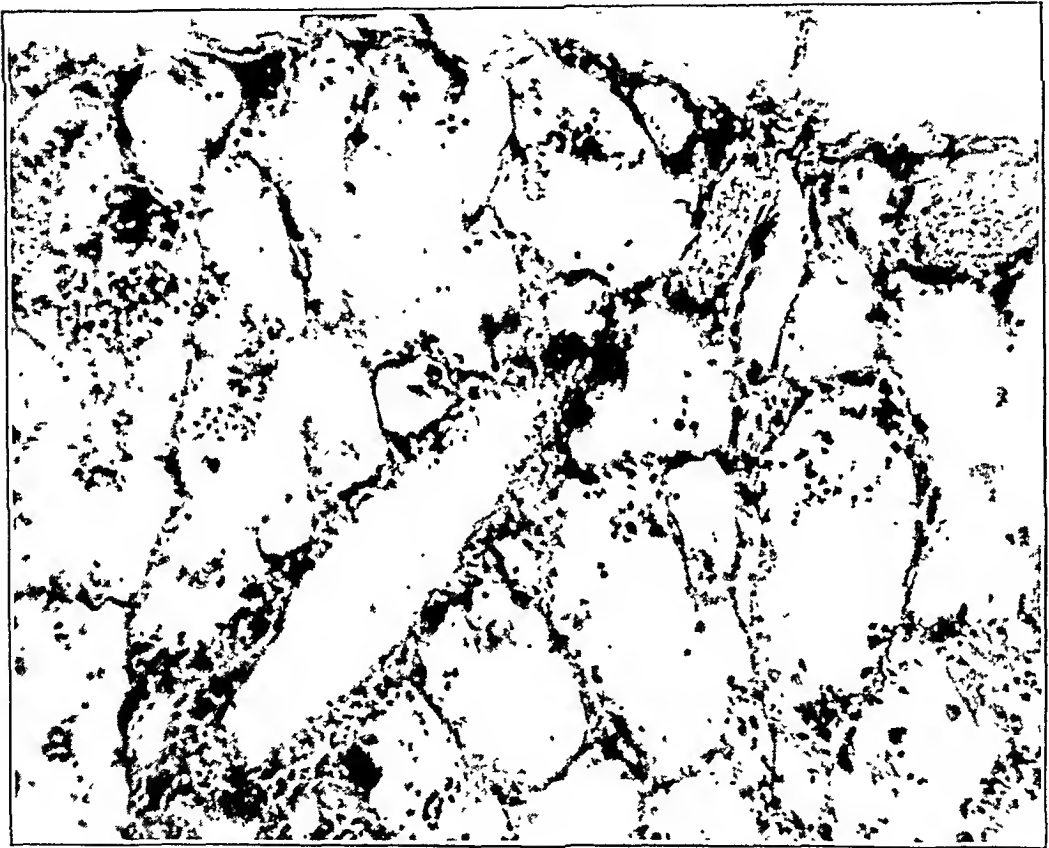


Fig. 9 (dog 496).—A portion of the area comprising figure 8 more highly magnified and showing diffuse pneumonitis.

#### COMMENT

In cases of clinical emphysema there is usually enlargement of the thorax together with a history of a chronic cough, with or without asthmatic symptoms. The pathologic condition is usually characterized microscopically by evidence of chronic inflammation attending the emphysematous changes, i. e., destruction of elastic and fibrous tissue

19. Drs. C. C. Macklin and Clayton G. Loosli gave criticism in the interpretation of the microscopic observations.

and the capillary structure of the alveolar walls. The degree of these inflammatory changes depends on the clinical course of the disease prior to the time of death, i. e., acute or chronic.

The results of these experiments are those following overdistention of the lung simulating repeated asthmatic attacks extending over several months. The elements of enlargement of the thorax and infection are eliminated with the exception of the inflammatory changes in dog 496. This pressure phenomenon in itself appears to have failed in the production of emphysema, although repeated overdistention for fifteen minutes biweekly over a period as long as eleven months was carried out. There was, however, moderate dilatation of the terminal respiratory units, i. e., the alveolar ducts and sacs, but no microscopic destruction of alveolar elements. The acute experiments, except in 1 old dog, resulted in interstitial and mediastinal emphysema, whereas in the chronic experiments which were terminated by acute study this phenomenon was absent or less marked. The explanation for this difference was probably on a basis of the repeated injury of the interstitial tissue during overinflation with subsequent fibrosis in the latter experiments. In sections of normal lung parenchyma the walls of the alveolar ducts between the alveolar sacs and the alveoli are made up of muscle cells and elastic and collagenous fibers. The latter elements appear as short knobs or clubs running parallel to the long axis of the duct.<sup>20</sup> We believe that these have been erroneously interpreted by some authors<sup>21</sup> as evidence of emphysematous changes.

In the case of dog 496, in which pneumonia was present, there was insufficient evidence to warrant drawing conclusions. It is most suggestive that the factor of infection when added to repeated overdistention is significant in the production of pulmonary emphysema. This is receiving further attention at the present time. Microscopic sections showing pulmonary emphysema resulting from tracheal obstruction and overdistention which have been presented by another author<sup>14</sup> strongly suggest a combination of infection and overdistention as the etiologic factor.

*Pressures.*—Periods of overinflation were routinely accompanied by a diminution in the systemic blood pressure to such a level that cyanosis was occasionally observed. This is similar to that sometimes seen clinically during asthmatic attacks. Accompanying this fall in systemic blood pressure was a marked rise in the peripheral venous pressure,

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20. Maximow, A. A., and Bloom, W.: *Textbook of Histology*, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 448.

21. Longacre, J. J., and Johansmann, R.: *An Experimental Study of the Fate of the Remaining Lung Following Total Pneumonectomy*, *J. Thoracic Surg.* **10**: 131-149, 1940.

indicating the increased resistance to the circulation in the lung and also the load placed on the right side of the heart during overdistention. This is similar to the changes occurring during an asthmatic attack and explains the development of hypertrophy and failure of the right side of the heart in persons with chronic asthma.

Mediastinal emphysema, air embolism and subpleural (and parenchymal) hemorrhage developed during overdistention in 2, or 22.2 per cent, of 9 dogs. This phenomenon might explain the cause of death in some asthmatic persons in whom heart failure or other definite cause is not evident.

Biweekly pulmonary overinflation alone with a pressure of 35 mm. of mercury over periods as long as eleven months failed to produce true emphysema in dogs.

The pressures used for overinflation were sufficient to cause marked lowering of the systemic arterial pressure and marked elevation of peripheral venous pressure and in 2 cases pulmonary air embolism and hemorrhage into the pulmonary parenchyma.

There were emphysematous changes of the parenchyma of the lung in 1 dog in which the factor of infection was added to that of overdistention.

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# GUMMATOUS AORTITIS

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Syphilitic disease of the aorta may occur in either of two forms, (a) as a productive scar-forming type of chronic aortitis or (b) as gummatous aortitis. The former is the usual manifestation of cardiovascular syphilis. Gummatous lesions of the aorta, on the other hand, are rarely observed, and this type of aortitis has not been studied extensively. It is the purpose of this communication to describe the clinical and the morphologic features of gummatous aortitis and to define the differential characteristics of this disease in relation to other diseases of the aorta.

This study was stimulated by observations made in the following 3 cases, which we are reporting in detail.

## REPORT OF THREE CASES

CASE 1.—C. C., a 35 year old Italian-born housewife, was admitted to the Boston City Hospital for the third time on Nov. 14, 1935. On entrance she was in a state of acute pulmonary edema, manifested by frothy bloody sputum, cyanosis, profuse perspiration and mild delirium. She did not respond to emergency treatment and died shortly after admission.

The patient had been well until July 1934, when she had begun to notice shortness of breath on mild exertion. Since that time she had also had a sense of constriction in the precordial region when she walked, but never while at rest. This distress would pass away soon after the cessation of activity. For approximately the same period (seventeen months) she would feel well on retiring, only to be awakened by severe attacks of nocturnal dyspnea which recurred three or four times during the night. Until six months before entry she had not noticed edema of dependent parts. Although a dry cough had been present, she had never noticed any blood-flecked sputum.

There was no history of pains in the joints, chorea or an unusual number of attacks of sore throat, although her tonsils had been removed the year before. She had undergone a cesarean section in 1931 and stated that at that time her blood was "all right." The patient stated, however, that she had had "bad blood" since the age of 20 and was treated with "shots" at that time. In January 1934 the patient

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† Deceased.

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was delivered of a premature baby, at which time she was found to have a positive serologic reaction for syphilis. She was referred to the outpatient department of the Massachusetts General Hospital for treatment. After four intramuscular and two intravenous injections of an antisyphilitic compound she did not return to the clinic.

The patient was admitted to the Boston City Hospital for the first time on July 6, 1934, with the complaint of inability to sleep because of attacks of "shortness of breath." Her ankles were markedly swollen. She had been nauseated but had not vomited. On conservative treatment the patient improved rapidly and was discharged on the twentieth day after admission, symptom free, only to return to the outpatient department three months later with the same complaint of inability to sleep because of choking attacks. She had been only "fairly well" since her discharge, even though she was on a restricted regimen and was taking digitalis. In the hospital she again improved and was discharged on the twenty-sixth day after entry with the recommendation of convalescent care, which she refused. It was on the fourth day after discharge that the patient returned to the hospital moribund and died in an attack of cardiac asthma with pulmonary edema.

*Clinical and Laboratory Data.*—The essential findings one month before her fatal attack included the following data: The patient was sallow, tired-appearing and fairly well developed and nourished. She was sitting upright in bed, breathing with difficulty. Her eyes, ears, nose and throat were not remarkable. Moderate venous congestion was present in the neck. There was flatness to percussion in the bases of both lungs, extending to the eighth vertebral spine on the left side, with flatness and markedly diminished breath sounds on the right side. The heart was greatly enlarged, with the left border of dulness in the anterior axillary line; the right border of dulness extended 4 cm. to the right of the sternum. At the apex the heart sounds were almost entirely replaced by continuous swishing systolic and diastolic murmurs; at the level of the second rib on the right there were a loud diastolic murmur replacing the second sound and a softer "hissing" systolic murmur. The aortic diastolic murmur was transmitted from the base of the heart almost to the apex. Along the left border of the sternum an inconstant thrill, diastolic in time, was also noted. There was a collapsing type of pulse, and the blood pressure was 150 mm. of mercury systolic and 50 mm. diastolic. The liver was slightly tender and palpable 2 fingerbreadths below the costal margin. The spleen was firm, nontender and palpable 3 fingerbreadths below the left costal margin. Otherwise the abdomen was normal. There was slight pitting edema below the knees. At the time of admission the patient was afebrile; the pulse rate was 85 per minute and the respiratory rate 20 to 24 per minute.

The urinary sediment was essentially normal. The specific gravity ranged from 1.007 to 1.019. The red cell count was 3,970,000 per cubic millimeter; the hemoglobin concentration, 86 per cent. The white cell count was 4,000 per cubic millimeter; the differential count showed 61 per cent polymorphonuclears, 32 per cent lymphocytes and 7 per cent monocytes. Kahn and Hinton reactions of the blood were positive. Per hundred cubic centimeters, the blood contained 35 mg. of nonprotein nitrogen and 5 Gm. of total protein and the albumin-globulin ratio was 2 to 1. A roentgenogram revealed the heart to be enlarged both to the right and to the left. On fluoroscopic examination there was a slight increase in the size of the right auricle, which appeared to pulsate during ventricular systole; therefore the presence of a tricuspid regurgitation was suspected. The

lungs were within normal limits. The electrocardiogram showed a normal rhythm, a rate of 100 per minute, a PR interval of sixteen hundredths of a second and a QRS interval of twelve hundredths of a second. The QRS was slurred in all leads. The T wave was upright in lead I, diphasic in lead II and inverted in lead III. The axis was normal. The interpretation was intraventricular block.

In addition to the usual treatment for congestive failure of the circulation, the patient was given potassium iodide and a few injections of an antisyphilitic compound.

Diagnosis: The diagnoses at the time of death were syphilitic heart disease with aortitis, aortic regurgitation and probably narrowing of the mouth of the coronary arteries; congestive heart failure with slight peripheral edema, chronic passive congestion of the liver and left hydrothorax; syphilitic splenomegaly, and cardiac asthma with terminal pulmonary edema.

*Necropsy.*—The heart (with part of the aorta) weighed 600 Gm. The epicardium was smooth and glistening. The myocardium was deep red and moderately firm. There was some hypertrophy of the left ventricular wall and dilatation of all the chambers. The valves of the right side of the heart were normal. There was slight thickening and shortening of the chordae tendineae of the median cusp of the mitral valve associated with lengthening of the corresponding papillary muscles. There were pearly gray, glistening, translucent, moderately firm nodules 1 to 3 mm. in diameter along the line of closure of the mitral valve. There was no scarring of the papillary muscles.

All of the aortic cusps were gray, firm and thickened, with an increase in thickness at the free margins. The cusps were contracted, and the commissures of all were separated. This was most marked between the anterior and the right posterior cusp, which were separated by a distance of 0.8 cm. The right half of the anterior cusp was detached at its base, allowing the cusp to flap as a tongue-like process. There was transverse white thickening of the ventricular endocardium beneath the anterior aortic cusp where it was detached. The endocardium of the left auricle and the left ventricle was thickened.

Valvular measurements were as follows: tricuspid 14.3 cm., pulmonary 8.5 cm., mitral 10.3 cm. and aortic 7.5 cm. The thickness of the left ventricle was 1.6 cm. and that of the right ventricle 0.3 cm.

The first 2.5 cm. of the ascending aorta was distinctly thickened by moderately firm tissue, the surface of which was pitted and gray except for one yellow area 1 cm. in diameter where the surface of the aorta was depressed (fig. 1). The right coronary opening ran through this area and was closed. The orifice of the left coronary artery lay 1.5 cm. above the level of the opening of the right one. There was slight narrowing of the lumen of the left coronary artery by heaping up of pearly gray tissue around its lower half. The coronary arteries beyond their orifices were normal. At the beginning of the aortic arch there was a round swelling 1.5 cm. in diameter which projected 0.4 cm. above the intimal surface. The surface was gray and pitted. The cut surface revealed a gray, glistening tissue, replacing the intima and apparently the media. Slightly yellow intimal thickening was encountered around the orifices of the great vessels from the aortic arch. In the descending thoracic aorta there were a few linear elevations similar in appearance to the round elevation at the beginning of the arch. Otherwise the aorta appeared normal and elastic and the intima smooth and glistening. The result of the examination of other organs was unessential.

**Anatomic Diagnosis:** The anatomic diagnoses were aortic endocarditis, probably syphilitic; mitral rheumatic valvulitis; complete occlusion of the right coronary artery and partial occlusion of the left one; focal aortitis, probably syphilitic; pulmonary congestion and edema, and bilateral hydrothorax.

**Histologic Examination.**—Heart: The muscle fibers were hypertrophied. A few small scars were scattered through the myocardium. Both the epicardium and the endocardium contained a small number of lymphocytes.

**Mitral Valve:** The leaflets were somewhat thickened due to rather cellular and edematous connective tissue.

**Aortic Valve:** The cusps were markedly thickened because of a large amount of relatively acellular, somewhat hyaline collagen. Vascular spaces were present, and about them occurred lymphocytes and plasma cells in varying numbers. The



Fig. 1 (case 1).—The aortic valve and adjacent aorta and left ventricle. The aortic leaflets are thickened and shrunk. Above the cusps are projecting nodular areas which represent the regions of the aorta involved by the gummatous mesoarteritis.

base of the valve and the adjacent endocardium showed a type of thickening similar to that of the cusps.

**Ascending Aorta:** The intima showed a nodular increase in connective tissue, some of which was evidently recently formed and quite cellular, while other areas consisted of dense collagen. In the thickened areas a few small blood vessels were present, and about some of them were occasional lymphocytes and plasma cells. The media contained foci of necrosis. At the periphery of such necrotic areas there was vascular connective tissue, heavily infiltrated with lymphocytes, plasma cells and some giant cells. In one or two such areas there were also some polymorphonuclear leukocytes. Elsewhere there were foci of extensive

scarring. Such scars were made up of vascular, rather cellular connective tissue infiltrated with plasma cells and lymphocytes. The adventitia showed pronounced thickening with dense connective tissue which was infiltrated with lymphocytes



Fig. 2 (case 1).—The media, showing an area of necrosis. Adjacent to this area is a focus of vascular connective tissue infiltrated with lymphocytes, plasma cells and some giant cells.

and plasma cells. The arteries showed a slight to marked degree of endarteritis obliterans.

Histologic Diagnosis: The histologic diagnoses were gummatous mesaortitis and healed endocarditis of the mitral and the aortic valve.

CASE 2.—J. M., a 35 year old Irish-American chauffeur, was admitted to the Boston City Hospital on June 9, 1936, with chief complaints of severe dyspnea, cough and edema of the legs. This was his ninth hospital admission since 1930.

At the age of 8 the patient had suffered from a severe attack of migrating polyarthritis, manifested by swollen and painful joints, sore throat, fever and nodules over his legs. He was kept in bed about three months. Between the ages of 8 and 14 he had been well except for occasional mild subacute painful swelling of certain joints. At the age of 14 he had had a short but severe attack of rheumatic fever and was in bed for fourteen days. During the following sixteen years he had felt well. In 1930, at the age of 30, he had had another attack of rheumatic fever, with malaise, fever, anorexia and pains in the joints, and had entered the hospital. The diagnoses were chronic rheumatic heart disease with aortic stenosis and insufficiency, mitral stenosis, cardiac decompensation, angina pectoris and Schönlein's purpura. The patient improved markedly under treatment.

In 1932 he had reentered the hospital, and in view of a positive reaction of the blood for syphilis, a syphilitic causation of the heart disease had been suggested. The suspicion was strengthened by finding gummatous lesions involving the soft palate and the fauces. The patient was given partial antisiphilitic treatment. On each of seven subsequent admissions, in addition to the rheumatic, the question of syphilitic causation of the heart disease had been discussed. The patient had entered the hospital on each occasion because of severe nocturnal paroxysmal dyspnea associated with angina pectoris.

The family history was noncontributory. The patient had married in 1925 and become divorced in 1927. His wife had had one miscarriage.

*Clinical and Laboratory Data.*—During the last admission, in 1936, the essential findings included the following data: The patient was in a high orthopneic position. His expression was anxious, and he was sweating profusely. Scarred atrophic areas were scattered on the fundi of both eyes. The nasal septum was perforated. Punched-out and scarred areas were present over the soft palate. The arteries of the neck showed pronounced pulsation. There was a severe, loud, rough systolic murmur over the carotid arteries. The veins of the neck were not distended. There was a prominent systolic heave over the left side of the thorax, and all the intercostal arteries were pulsating. The apical impulse was in the fifth interspace in the midaxillary line. There was a marked thrill over the second right intercostal space. At the apex a loud crescendo presystolic murmur was heard. This was followed by a rough systolic, and by a long blowing softer diastolic, murmur. All three murmurs were well transmitted into the axilla. Over the aortic area there was a rough loud systolic murmur corresponding to a systolic thrill and a blowing diastolic murmur. The diastolic murmur was heard with clarity all over the precordium. The aortic systolic murmur was transmitted to the neck. The pulses were of water-hammer character, and a clear Duroziez murmur was present. The arterial pressure in the arm was 155 mm. systolic and 45 mm. diastolic and in the leg 230 mm. systolic and 40 mm. diastolic, measured in millimeters of mercury. No other abnormalities were present.

During his last stay in the hospital the urine was normal. There was no anemia or leukocytosis. The Hinton reaction of the blood was positive. Electrocardiograms revealed no change from the condition observed on previous admissions.

The patient improved under treatment, but an attack of acute dyspnea and cyanosis developed, and he died within five minutes after the onset of the attack.

**Diagnosis:** The diagnoses included rheumatic and syphilitic heart disease with aortic stenosis and insufficiency, mitral stenosis and insufficiency, congestive failure of the circulation, angina pectoris, syphilitic chorioretinitis and tertiary syphilis.

**Necropsy**—The pericardial cavity was completely obliterated by old fibrous adhesions, which after removal left a rough and irregularly hemorrhagic visceral pericardium. The heart weighed 780 Gm. The pulmonary, tricuspid and mitral valves were entirely normal. The left ventricle was markedly dilated and the wall hypertrophied, with a thickness of 2.2 cm. About 1 to 2 cm. below the aortic valve was a linear fibrous thickening (Zahn's pocket). The aortic valve was dilated and showed marked thickening of the free margins of the cusps. In addition, between the left anterior and the posterior cusp there was about 0.15 cm. of separation, while the remaining adjacent portions of the cusps were fused. This was most



Fig. 3 (case 2).—Gummatous mesaortitis. There is a large area of destruction of the media with a focus of caseation necrosis. The remainder of the defect in the media is filled with connective tissue densely infiltrated with lymphocytes, plasma cells and giant cells.

marked between the right posterior and the anterior cusp. The coronary orifices were widely patent. The right ventricular wall was moderately hypertrophied and measured 0.5 cm. The circumferences of the cardiac orifices were as follows: tricuspid valve 11.6 cm., pulmonary valve 7.5 cm., mitral valve 11.2 cm. and aortic valve 8.5 cm.

The aorta was normal except for the ascending portion of the arch. Here there were elevated, irregular, flat, yellowish white and somewhat soft patches 4 to 6 mm in diameter. The rest of the aorta was essentially normal.

**Anatomic Diagnosis:** The anatomic diagnoses were syphilitic aortitis with involvement of the aortic valve, healed aortic valvulitis, cardiac dilatation and hypertrophy and pulmonary congestion and edema.

*Histologic Examination.*—Heart: The muscle fibers were hypertrophied. Both the epicardium and the endocardium contained an increased amount of collagen. In the endocardium were several focal collections of large, mononuclear cells with basophilic cytoplasm. These cells were arranged tangentially along strands of collagen. There were some lymphocytes at the periphery of these areas. Similar smaller focal collections of these large basophilic cells could be found in the region of the blood vessels in the myocardium. These focal lesions had all the characteristics of Aschoff bodies. There were in addition scattered polymorphonuclear leukocytes about the myocardial vessels.

Aortic Valve: The cusps contained a large amount of acellular collagen. Blood vessels were fairly numerous and showed a varying degree of perivascular infiltration with lymphocytes and histiocytes. In one cusp near the base there was an area of necrosis. Surrounding this were numerous histiocytes and giant cells. The necrotic material contained nuclear debris.

Aorta: The intima showed marked thickening with cellular connective tissue which was infiltrated with some fatty macrophages and lymphocytes. The media was interrupted by scars made up of vascular connective tissue infiltrated with lymphocytes and plasma cells. In addition, there were fairly numerous foci of necrosis. These necrotic areas were surrounded by large mononuclear cells, giant cells, lymphocytes and plasma cells. The adventitia was thickened and contained bundles of rather dense collagen. The vasa vasorum showed varying degrees of endarteritis obliterans, and many had a perivascular infiltration of lymphocytes and plasma cells (fig. 3). Sections of the heart, the aortic valve and the aorta stained by Levaditi's method gave negative results. The rest of the histologic data were unessential.

*Histologic Diagnosis:* The histologic diagnoses were gummatous mesaortitis, healed endocarditis and gummatous endocarditis of the aortic valve and rheumatic myocarditis.

CASE 3.—The specimens in this case, in which the patient was a 42 year old housewife who died suddenly, were furnished us by Dr. Timothy Leary, Medical Examiner for Suffolk County, Boston. This patient had enjoyed good health except for complaints of soreness over the epigastrium and pains about the heart for two years previous to her sudden death. She had walked into the house of friends, vomited blood and fallen to the floor unconscious. She was rushed to the hospital but was dead on arrival.

*Necropsy.*—The heart weighed 220 Gm. The myocardium was brownish red. All the valves were normal. The measurements were as follows: tricuspid valve 10.5 cm., pulmonary valve 5.4 cm., mitral valve 9.1 cm. and aortic valve 5.2 cm. The thickness of the left ventricle was 1.7 cm. and that of the right ventricle 0.3 cm. There was a marked narrowing of the orifices of both the right and the left coronary artery.

The proximal 5 cm. of the aorta showed a rough intima with numerous slightly raised, pearly gray nodules which varied from 3.0 to 8.0 mm. in diameter. Between the aorta and the pulmonary artery was a mass of firm tissue, measuring 3.0 by 2.0 by 1.5 cm. On section this tissue was grayish in color with yellowish areas. This mass protruded into the lumen of the pulmonary artery at several points, extending 2.0 to 4.0 mm. above the intimal surface, which was apparently intact. These projections had a smooth, lobulated surface and were yellowish white. There was a small, saccular aneurysm of the aortic arch in its superior posterior portion. This



aneurysm lay between the innominate and the left common carotid artery (fig. 4). A short tract led from the depth of this aneurysm into the trachea, 2 cm. above its bifurcation. The tracheal mucosa in this region was greenish red and was ulcerated over an area 0.8 cm. in diameter, although the perforation was pinpoint in size (fig. 5). The external surface of the aortic arch was covered with firm gray tissue. The descending aorta was normal save for a few small yellowish plaques.



Fig. 4 (case 3).—The descending aorta and an aneurysm of the transverse portion. Both above and below the opening of the aneurysm is seen an extensive granulomatous involvement of the mediastinal tissues with numerous gummas.

The right lung weighed 550 Gm. The external surface was dark red, smooth and glistening. The upper lobe had a firm, rubbery consistency. Its cut surface was dark red, and a small amount of pink, frothy fluid could be expressed. The middle and lower lobes were essentially similar to the upper lobe.

Anatomic Diagnosis: The anatomic diagnoses were aneurysm of the aorta with perforation into the trachea and syphilitic aortitis.

*Histologic Examination.*—The myocardium was normal. Sections through the left coronary artery showed some fibrous thickening of the intima.

There were foci of necrosis in the media of the ascending aorta typical of gummatous mesaortitis, as described in the 2 preceding cases. The adventitia showed fibrous thickening with marked perivascular infiltrations of lymphocytes and plasma cells around the vasa vasorum, which showed various degrees of endarteritis obliterans. The intima exhibited atheromatous changes. Sections of the aneurysm at its point of rupture into the trachea showed extensive necrosis consistent with gumma. The trachea at this point exhibited thickening of the submucosa due to



Fig. 5 (case 3).—The trachea, showing the point of rupture of the aortic aneurysm.

granulation tissue and an infiltration of numerous lymphocytes and plasma cells. There was, in addition, an area of necrosis with ulceration of the overlying epithelium.

The mass of tissue lying between the aorta and the pulmonary artery was composed of granulation tissue with numerous areas of infarct necrosis. Giant cells were numerous, and there was a marked infiltration of lymphocytes and plasma cells. This granulomatous process had invaded and destroyed the adventitia and the media and had involved to a marked degree the intima of the pulmonary artery. The masses projecting into the lumen of the pulmonary artery

described in the gross examination were composed of this gummatous granulation tissue. The endothelium lining the vessel was intact. The vessel wall where it was not invaded by this granulomatous tissue showed no changes.

**Histologic Diagnosis:** The microscopic diagnoses were gummatous mesaortitis and gummatous mediastinitis with involvement of the pulmonary artery.

#### MATERIAL STUDIED AND ADDITIONAL CASES

As a result of the study of these 3 cases a systematic study of gummatous aortitis was undertaken. The material used came from the departments of pathology of the Boston City Hospital and the Massachusetts General Hospital. A total of 360 cases of syphilitic aortitis were studied, 186 cases from the former, and 174 from the latter, institution. All cases in which necrosis was evident were investigated in detail. Gummatous aortitis, as its name implies, is characterized by gumma formation, usually in the media. In our series the gummas were usually of miliary type and could be definitely recognized only microscopically. They occurred as areas of necrosis involving both muscle and elastic tissues. The necroses either were of the infarct type, i. e., the outlines of the preexisting structures could be recognized in the necrotic areas, or were composed of structureless material containing nuclear debris. Calcification of such necrotic foci did not occur. The form of the medial gummas conformed to the structures of the media, being roughly quadrangular or oval in shape. At the periphery of such gummas were broad sheets of vascular granulation tissue which was heavily infiltrated with lymphocytes, plasma cells and some large mononuclear cells. Giant cells were present, usually in close proximity to the necrotic material.

The adventitia showed marked thickening due to increased connective tissue, which was infiltrated with numerous lymphocytes and plasma cells, especially in the neighborhood of the vasa vasorum. These vessels often showed varying degrees of endarteritis obliterans. Occasionally gumma formation occurred in the adventitia (fig. 6). The intima usually showed varying degrees of fibrosis, often focal in distribution.

The atheromatous changes observed in our large group of cases of chronic syphilitic aortitis were usually pronounced over the parts affected by syphilis, suggesting that the syphilitic process had enhanced the development of intimal atheromas. A similar view has been expressed recently by Leary.<sup>1</sup>

There were 8 cases of gummatous aortitis in 360 cases of aortitis. In 2 additional cases the histologic changes were suggestive, but no definite diagnosis could be made. Obviously, the frequency ratio of 1:45 must be considered as minimal, in view of the fact that the finding

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1. Leary, T.: Syphilitic Aortitis as Cause of Sudden Death, *New England J. Med.* **223**:789-793, 1940.

of gummas was not based on a study of systematic serial sections of the arch of the aorta.

The ages of the patients in these 8 cases of gummatous aortitis varied between 32 and 59. Five patients were men, and 3 were women. Five of the patients had aortic insufficiency. Paroxysmal cardiac dyspnea was present in 5 cases. The immediate cause of death was usually pulmonary edema. It is of especial interest that in 1 case a patient had also suffered from rheumatic fever.

The clinical features in these cases of gummatous aortitis are not specific or characteristic. The clinical manifestations, such as dyspnea, orthopnea, precordial distress, cardiac asthma and pulmonary edema,



Fig. 6.—A gumma in the adventitia of the aorta.

are attributable to the presence of aortic insufficiency or narrowing or occlusion of the coronary arteries. The two last-named changes may be caused by the gummatous syphilitic lesion, as was true in 1 of the cases observed by us (case 1). Clinical diagnosis of gummatous aortitis is difficult or even not feasible. The coexistent rheumatic condition, however, may raise suspicion, for it seems more than a coincidence that in 3 of the 11 cases studied by us the patients had also suffered from rheumatic fever.

In 3 additional cases of chronic syphilitic aortitis massive destruction of the aortic wall was present. These lesions contained polymorphonuclear leukocytic infiltration, a picture not unlike an abscess. In these cases the lesions were not considered as being gummatous. Three possibilities of causation were considered in these cases: first, that the acute destructive lesions were the result of syphilis alone; second, that

they were the result of a secondary invading infection superimposed on syphilitic aortitis, as reported by Rappaport<sup>2</sup> and by Saphir and Cooper,<sup>3</sup> and third, that they were unrelated to syphilis.



Fig. 7.—Acute aortitis. Infiltration of the intima with polymorphonuclear leukocytes is evident.

In order to determine whether similar acute abscess-like lesions are found in aortas of nonsyphilitic subjects, the records and the histologic

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2. Rappaport, B. Z.: Primary Acute Aortitis, *Arch. Path.* 2:653-658 (Nov.) 1926.

sections of the aortas in 224 control cases in which death occurred from a variety of causes were examined for focal acute aortitis of the type observed in these cases of syphilis. Six cases of acute nonsyphilitic aortitis were collected. In 1 case it occurred in a patient with mediastinitis, in 4 in patients with medionecrosis idiopathica cystica and in 1 in a patient with lymphatic leukemia (fig. 7). It is therefore concluded that the occurrence of such acute abscess-like lesions of the aorta is unrelated to syphilitic aortitis, though it is probable that syphilitic aortitis and other chronic conditions in the aorta predispose to the development of secondary acute aortitis.

#### DIFFERENTIAL MORPHOLOGIC CHARACTERISTICS OF ACUTE LESIONS OF THE AORTA

There are a number of other acute diseases of the aorta, which it is essential to differentiate from gummatous aortitis.

*Acute Bacterial Aortitis.*—Acute lesions with abscess formation of the intima of the aorta are on the whole uncommon and when they do occur are usually secondary to infectious lesions of the cardiovascular system elsewhere, most commonly endocarditis. An extremely rare form, termed primary acute aortitis by Rappaport,<sup>2</sup> occurs without other infectious lesions of the vascular system being present. It is generally agreed that a preexisting lesion of the aorta, especially an atherosclerotic lesion, predisposes to bacterial invasion of the intima. However, Rappaport<sup>2</sup> and Saphir and Cooper<sup>3</sup> have reported single cases of acute aortitis superimposed on syphilitic aortitis. The occurrence of acute bacterial aortitis superimposed on atherosclerosis or on syphilitic aortitis may be looked on as being analogous to the occurrence of abscesses in previously damaged or diseased myocardium or voluntary muscle.<sup>4</sup> On the basis of a study of the literature, Rappaport stated that previous pathologic changes, whether atherosclerotic or syphilitic, predispose to acute infection of the wall of the aorta either through direct implantation of its surface or through the vasa vasorum. However, the presence of a concomitant acute inflammation does not influence the histologic picture of syphilitic aortitis.

In our series we encountered 1 case of acute bacterial aortitis secondary to pneumococcic endocarditis of the tricuspid valve, occurring in an atheromatous plaque (fig. 8).

*Rheumatic Aortitis.*—The lesions of rheumatic fever usually are located in the adventitia and media but may also involve the intima. In the acute stage the vasa vasorum show swelling of their endothelium,

3. Saphir, O., and Cooper, G. W.: Acute Suppurative Aortitis Superimposed on Syphilitic Aortitis, *Arch. Path.* 4:543-545 (Oct.) 1927.

4. Weiss, S., and Wilkins, R. W.: Myocardial Abscess with Perforation of the Heart, *Am. J. M. Sc.* 194:199-204, 1937.

and there is a scattered infiltration in the adventitia of lymphocytes, plasma cells and large mononuclear cells, some of which are Aschoff cells. In the media at this stage numerous Aschoff cells may be found,



Fig. 8.—Acute bacterial aortitis. Spaces in the intima contain masses of pneumococci.

arranged in rows between the elastic fibers. The nutrient vessels in the media show intimal swelling. There is a varying amount of perivascular infiltration of lymphocytes, plasma cells, polymorphonuclear leukocytes

and large mononuclear cells. The collagen adjacent to the vessels shows swelling and degeneration.

In the later active, or in the healed, stage the connective tissue of the adventitia is thickened and dense and contains scattered lymphocytes and plasma cells. In addition, Aschoff cells may be present and may have a focal arrangement suggesting Aschoff nodules. In the media there are avascular, collagenous scars in the areas in which the nutrient vessels normally occur, namely, the outer third.

*Tuberculosis of the Aorta.*—This is on the whole an uncommon lesion of the aorta. Usually the involvement occurs from extension of a tuberculous process from neighboring structures. More rarely it arises in the intima from a hematogenous infection. Histologically, the lesions show the usual picture of tuberculosis, either the caseous or the miliary type.

*Atherosclerotic Necrosis.*—The necrosis associated with atherosclerosis is situated primarily in the intima, although some extension into the adjacent media may occur. The necrotic areas either represent the late stage of a previously lipoid-filled focus or occur in the deeper portions of healed, fibrous plaques. The lesions appear under low magnification as pale, essentially unstained areas. Under high magnification these areas are found to consist of anuclear material with no definite structure. Clefts representing cholesterol crystals are frequently present in varying numbers. No cellular reaction to such areas of necrosis is present to any degree.

*Medionecrosis Idiopathica Cystica.*—In this condition the media shows foci of basophilic-staining material in which the muscle and the elastic fibers have disappeared. There is no cellular reaction to such areas of necrosis. In certain instances, probably as a later stage of the lesion, cysts filled with mucinous-like material are found.

*Aortitis of Undertermined Origin.*—Certain cases of mesaortitis have been described from time to time, the causation of which has been entirely obscure. The conditions in these cases do not fit into any of the types just described.<sup>5</sup> Dr. T. B. Mallory, of the Massachusetts General Hospital, recently gave us the opportunity to study 2 striking examples of aortitis of this class. In both cases the patients were young, with no history or clinical or serologic evidence of syphilis.

Histologic examination revealed the following: The intima was thickened because of an increased amount of connective tissue, which in places was rather myxomatous in character. In this thickened intima thin walled vascular channels occurred. The media was greatly scarred and distorted. In some areas the normal elements of the media had

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5. Sproul, E. E., and Hawthorne, J. J.: Chronic Diffuse Mesaortitis: Report of Two Cases of Unusual Type, *Am. J. Path.* **13**:311-323, 1937.



entirely disappeared, being replaced by cellular, vascular connective tissue which was infiltrated by lymphocytes, plasma cells and macrophages. Some foci of necrosis were present, and calcification of necrotic material had taken place in several areas. The adventitia showed marked thickening with dense, rather hyaline collagen, which contained scattered lymphocytes and plasma cells. Several adventitial vessels showed slight to moderate degrees of intimal proliferation. It is obvious that the histologic structure of this aortitis differs essentially from that of gummatous aortitis.

#### COMMENT

Prior to the identification of *Spirochaeta pallida* as the causative agent of syphilis, cardiovascular manifestations of the disease were not thought to be common. The reason for this is that the "gumma" was considered the essential lesion of late syphilis, and when it was absent the diagnosis of syphilis was uncertain. The diagnosis of gumma of the aorta was rarely made prior to 1903. The lesion is not discussed in some of the standard textbooks; in others there are contradictory statements as to the frequency of occurrence. Kaufmann,<sup>6</sup> Aschoff,<sup>7</sup> Bell<sup>8</sup> and other pathologists referred to gumma of the aorta without giving statistical evidence. Some pathologists spoke of "miliary gumma" of the aorta, and one is led to believe that this represents an early stage in the development of the usual picture of aortitis.<sup>9</sup> Such was the belief expressed by Martland,<sup>10</sup> who stated:

Acquired syphilis is essentially a supralvalvular sclerosis which may manifest itself in one of several ways. . . . We speak of the process as a sclerosis because the lesion found at autopsy is a deforming defect which has been following previous gummatous infiltrations.

He stated further:

The process in syphilis never heals completely. In some cases the lesion may remain distinctly gummatous and the involved area soft.

McMeans<sup>11</sup> spoke of "gummatous necrosis" of the medial coat as a common finding, although he did not mention its frequency, nor did he

6. Kaufmann, E.: *Lehrbuch der speciellen pathologischen Anatomie für Studierende und Ärzte*, ed. 9 and 10, Berlin, Walter de Gruyter & Co., 1931, vol. 1, pp. 114-115.

7. Aschoff, L.: *Pathologische Anatomie*, ed. 7, Jena, Gustav Fischer, 1928, vol. 2, pp. 79 and 80.

8. Bell, E. T.: *A Text-Book of Pathology*, ed. 4, Philadelphia, Lea & Febiger, 1941, p. 206.

9. Von Glahn, W. C.: *Cardiovascular Syphilis: Pathology*, in Nelson Loose Leaf Medicine, New York, Thomas Nelson & Sons, 1932, vol. 4, p. 341.

10. Martland, H. S.: *Syphilis of the Aorta and Heart*, *Am. Heart J.* **6**:1-29, 1930.

11. McMeans, J. W.: *The Localization of the Luetic Virus in the Aorta*, *Am. Heart J.* **6**:42-55, 1930.

describe the diagnostic criteria. Peck,<sup>12</sup> in a review of the international literature up to 1927, collected 29 cases of syphilitic involvement of the pulmonary artery, but in only 12, including 1 reported by the author, can the diagnosis be considered as absolutely certain. In 3 cases there were gummatous lesions, and in 2 cases there also were gummas of the aorta. He pointed out that syphilis of the aorta is manifested in two ways, one of which is the gumma, and stressed that "the macroscopic gumma is its characteristic form." In speaking of the cellular infiltration around the nutrient vessels in the adventitia and newly formed channels in the outer portion of the media, Warthin<sup>13</sup> stated that these infiltrations are often large enough to be regarded as miliary gummas, but the development of well defined gummatous nodules with caseating centers and giant cells is rare. When they do occur, they are usually multiple.

In a study of 126 cases of syphilitic aortitis Clawson and Bell<sup>14</sup> encountered 3 cases of gumma of the heart, but no mention was made of an aortic gumma. Winternitz,<sup>15</sup> Wright-Smith,<sup>16</sup> Renner<sup>17</sup> and Šikl<sup>18</sup> each reported a case in which there was postmortem evidence of gummatous aortitis. It is of interest that an examination of the cases of gummatous myocarditis reported in the literature indicates that gummatous aortitis was absent. Contrariwise, in the cases of gummatous aortitis studied by us and reported in the literature, gummatous myocarditis did not coexist.

Thus both our experience and a study of the literature indicate that true macroscopic gummatous aortitis, such as occurred in the 3 cases reported here, is rare. Although such a condition is referred to in textbooks on pathology,<sup>18</sup> a study of detailed reports indicates that the total number of adequately described cases reported in the literature, including the 3 described here, does not exceed 10. The condition, however, must be more common than indicated by the literature. Miliary

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12. Peck, S. M.: Pathologic Anatomy of Syphilis of the Pulmonary Artery: Report of Case and Review of Literature, *Arch. Path.* **4**:365-379 (Sept.) 1927.

13. Warthin, A. S.: The New Pathology of Syphilis, *Am. J. Syph.* **2**:425-452, 1918.

14. Clawson, B. J., and Bell, E. T.: Heart in Syphilitic Aortitis, *Arch. Path.* **4**:922-936 (Dec.) 1927.

15. Winternitz, M. C.: The Pathology of Syphilitic Aortitis with a Contribution to the Formation of Aneurysms, *Bull. Johns Hopkins Hosp.* **24**:212-216, 1913.

16. Wright-Smith, R. J.: Gummata of the Aorta with Rupture into the Pericardium, *J. Path. & Bact.* **31**:585-586, 1928.

17. Renner, C.: Gummöse Aortenentzündung infolge erworbener Syphilis beim Jugendlichen (Arteriitis gummosa), *Ztschr. f. Kreislaufforsch.* **26**:807, 1934.

18. Šikl, H.: Ungewöhnliche Ursache des plötzlichen Todes bei Aortenlues: frisches Gumma mit positivem Spirochätenbefund an der Abgangsstelle der linken Kranzschlagader, *Centralbl. f. allg. Path. u. path. Anat.* **57**:228-232, 1933.

gumma found on microscopic examination of the aorta, on the other hand, occurs more frequently. In our series it was encountered once in 45 cases of chronic syphilitic aortitis, and, as we indicate, this ratio is minimal. Whether in all cases of chronic syphilitic aortitis the lesions go through the microscopic gummatous stage at one time in their development cannot be stated.

The symptomatology of macroscopic or microscopic gummatous aortitis is not specific. Lesions of the wall of the arch of the aorta without perforation, aneurysmal dilatation or involvement of the coronary arteries or the aortic valve is not responsible for symptoms. If gummatous lesions, on the other hand, occlude the coronary arteries, such symptoms as pain, dyspnea, cardiac asthma or pulmonary edema can develop.

The diagnosis of gummatous aortitis can be suspected only in rare instances in young persons without aortic insufficiency but with a history of syphilitic infection in whom thoracic pain and rapidly progressing heart failure are associated with attacks of cardiac asthma and pulmonary edema. At times gumma of the aorta occluding the coronary arteries can be responsible for sudden death. This happened in the case reported by Šikl.<sup>18</sup> Occlusion of the coronary arteries by gumma of the aorta occurred also in the case reported by Renner<sup>17</sup> and in case 1 in our series.

It is of interest that in 2 of the 3 cases of macroscopic gummatous aortitis reported by us rheumatic lesions of the heart coexisted. Similarly in the case reported by Renner<sup>17</sup> rheumatic heart disease coexisted with gummatous aortitis. Sohval<sup>19</sup> reported 2 cases of gumma of the myocardium. In 1 of these cases both rheumatic and syphilitic lesions were present. One wonders whether the existence of these rheumatic lesions is a mere coincidence. The question is raised as to whether rheumatic fever, which is prone to produce an acute cellular hyperergic reaction in the myocardium or in the root of the aorta, enhances the tendency to the development of gummas, particularly in patients who have received but partial antisiphilitic treatment. The latter was the situation in cases 1 and 2 in our group. The significance of the combination of syphilitic and rheumatic heart disease has been discussed by several writers, including Lisa and Chandlee<sup>20</sup> and Swanson.<sup>21</sup>

Case 3 was unusual insofar as there were large syphilitic gummatous lesions located between the aorta and the pulmonary artery. These lesions were responsible for the perforation of the aorta into the trachea.

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19. Sohval, A. R.: Gumma of the Heart: Report of Two Cases, *Arch. Path.* **20**:429-444 (Sept.) 1935.

20. Lisa, J. R., and Chandlee, G. J.: The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection, *Arch. Int. Med.* **54**:952-980 (Dec.) 1934.

21. Swanson, H.: Combined Syphilitic Aortitis and Rheumatic Disease of the Heart: Report of Four Cases, *Am. Heart J.* **18**:672-683, 1939.

This is the only case with which we are familiar in which gummatous aortitis was associated with a small aneurysm of the aorta. In 1927 Peck<sup>12</sup> was able to collect from the literature but 2 cases of similar occurrence in which gumma of the aorta and of the pulmonary artery coexisted.

#### SUMMARY

Three cases of macroscopic gummatous aortitis are reported. In case 1 the gummatous process of the aorta completely occluded the right coronary artery and partially occluded the left one. In case 2 gummatous lesions were present also at the base of the aortic valve. In case 3 an extensive gummatous process affected not only the aorta but the pulmonary artery; the necrotic gummatous lesions resulted in perforation of the aorta into the trachea. In none of these 3 cases was there gumma in the myocardium.

Gummatous aortitis is mainly localized in the media, but usually the adventitia and the intima are also affected. Macroscopic gummatous aortitis is rare, and the number of authentic cases described in the recent literature, including the 3 described by us, totals less than 10. In addition to the case reported here of occlusion of the coronary arteries by gumma, only 2 cases of this condition were found in the literature.

Gummatous lesions of the aorta are responsible for symptoms only if they lead to narrowing or occlusion of the coronary arteries or to perforation of the aorta. Dyspnea, orthopnea, precordial distress, cardiac asthma, pulmonary edema and hemoptysis, when present, are referable to such lesions of the coronary arteries or the aorta.

Of 360 cases of chronic syphilitic aortitis, microscopic gummas occurred in 8 (1:45). This ratio must be considered minimal. Whether in all cases of chronic aortitis the lesions go through a stage of microscopic gummatous aortitis is not known.

In 3 of the 360 cases of chronic syphilitic aortitis an acute abscess-like lesion was encountered. In a control group of 224 cases similar "acute aortitis" occurred in 6 cases (in 1 associated with mediastinitis, in 1 with lymphatic leukemia and in 4 with medionecrosis idiopathica cystica). Chronic lesions of the aorta predispose to secondary acute abscess-like lesions.

The differential morphologic characteristics of gummatous aortitis, on the one hand, and those of acute bacterial aortitis, rheumatic aortitis, tuberculosis of the aorta, atherosclerotic necrosis, medionecrosis idiopathica cystica and aortitis of undetermined origin, on the other hand, are described.

In the group of 360 cases of chronic syphilitic aortitis, atheromatous changes over the area affected by the syphilitic lesions were prominent. This suggests that chronic syphilitic lesions of the aorta predispose to the development of local atherosclerosis.

# CONGO RED TEST FOR AMYLOID DISEASE

## A QUANTITATIVE TECHNIC

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Prior to the demonstration by Bennhold<sup>1</sup> that a diagnosis of amyloid disease could be based on the selective affinity of deposits of this substance within the body, any decision as to the presence of amyloid deposits in the body rested on presumptive data. In another article we<sup>2</sup> have presented cases that we have encountered in which this test was of service in arriving at a diagnosis. Even our restricted data demonstrate the utility of this little known test. Bennhold's original technic of the injection of 10 cc. of a 1 per cent congo red solution has been used since his method first appeared.<sup>3</sup> While our work was in progress Friedman and Auerbach<sup>4</sup> and later Taran<sup>5</sup> eliminated the factor of possible hemolysis by precipitating proteins with alcohol and (according to Taran) with acetone.

## METHOD

*Technic.*—We have made several modifications and refinements in the technic of performing this test, which yields information concerning the rate of removal of congo red from the blood stream. In place of using a stated amount of the dye for each patient, we have selected a dose graded according to the patient's weight: 4 mg. per kilogram of body weight.

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1. Bennhold, cited by Harmon and Kernwein.<sup>2</sup>

2. Harmon, P. H., and Kernwein, G.: Utility of the Congo Red Test in Diagnosis and in Differential Diagnosis, *Arch. Int. Med.*, this issue, p. 421.

3. Bookman, A., and Rosenthal, J., cited by Harmon and Kernwein.<sup>2</sup> Barker, N. W., and Snell, A. N., cited by Harmon and Kernwein.<sup>2</sup> Shapiro, P. F., and others, cited by Harmon and Kernwein.<sup>2</sup> Rosenblatt, M.: Amyloidosis and Amyloid Nephrosis, *Am. J. M. Sc.* **186:558**, 1933; The Clinical Manifestations of Amyloidosis, *Ann. Int. Med.* **8:678**, 1934.

4. Friedman, M. M., and Auerbach, O.: An Improved Congo Red Test for Amyloidosis, *J. Lab. & Clin. Med.* **21:93**, 1935.

5. Taran, A., cited by Lipstein, S., and Auerbach, O.: An Evaluation of the Congo Red Test for Amyloidosis, *Quart. Bull., Sea View Hosp.* **2:120**, 1937.

Four minutes and one hour after injection of this quantity of dye samples of blood are regularly removed for examination. If the presence of amyloid disease is suspected, intermediate specimens should be obtained. When the quantity of amyloid is large, as indicated by the presence of a palpable spleen and/or liver, we obtain samples of blood nine and fourteen minutes after injection. Not infrequently under these circumstances one or both of the specimens show only a trace of the dye remaining. Just prior to injection of the dye 10 cc. of blood is drawn, as a source of plasma for preparation of the usual standards, as described later. Any hemolysis is detected in this control, and if it occurs the whole test is repeated. To prevent coagulation 1.4 per cent sodium oxalate solution in distilled water is mixed with the blood withdrawn in the proportion of 1 volume of oxalate solution to 4 volumes of blood. Five cubic centimeters of oxalated blood (1 cc. of oxalate solution and 4 cc. of blood) is the usual sample. The specimen of blood is then centrifuged, and the oxalated plasma is drawn off the underlying corpuscles.

*Standards.*—These are made from an aqueous stock solution of 0.05 per cent congo red. Two cubic centimeters of oxalated plasma prepared prior to injection of the dye is placed in each of two 10 cc. volumetric flasks. There are then added varied quantities of the stock congo red solution, usually 0.3 and 0.2 cc. These standards, when diluted with distilled water to the mark on the flask, contain, respectively, 15 and 10 micrograms of congo red per cubic centimeter, calculated on the basis of the oxalated plasma prior to dilution. If amyloid disease is indicated by the test, even the specimen of blood drawn four minutes after injection will contain a reduced concentration of the dye, as compared with a similar specimen from a normal person, so that standard solutions for comparison are then prepared with 0.1 and 0.05 cc. of the dye in 2.0 cc. of oxalated, uncolored plasma, each mixture being diluted with distilled water in a 10 cc. volumetric flask, as previously described. These standards contain, respectively, 1.5 and 2.5 micrograms of congo red per cubic centimeter.

*Calculations.*—The various specimens of blood are then compared with the appropriate standards by means of the colorimeter. The concentration of congo red in each specimen of original blood plasma can then be calculated by the following formula, in which  $S$  = micrograms per cubic centimeter of congo red in the diluted standard:  $S \times 1.25 \times 5$  = the concentration in micrograms per cubic centimeter of congo red in the original circulating blood. The percentage of dye left in the blood stream after one hour as compared with that present after four minutes can also be readily calculated. Check comparisons have shown that the maximum error is about 10 per cent, the average error being between 5 and 8 per cent, when oxalated blood is compared with standards prepared as described. The test is preferably done in the morning prior to the ingestion of the first meal of the day, so that alimentary lipemia will not be a disturbing factor in the colorimetric comparisons. If this is not possible, the test can be made five or six hours after the last previous meal. A sample of blood taken promptly after the ingestion of a meal cannot be accurately compared with one taken an hour later. In about one fourth of the patients having amyloidosis that we have encountered there is a slight shift toward an orange color in the specimens withdrawn after the dye has been in the blood stream, which renders the unknown samples not quite so suitable for comparison to the standards. Although error is introduced under such circumstances, the additional amount is not great. That this phenomenon is not due to blood hemolyzed during centrifugalization is controlled by the color of the sample of plasma obtained prior to dye injection.

When one has determined that the dye has all disappeared from the circulating blood stream in less than one hour and that appreciable amounts of amyloid are present, determination of the disappearance time of the dye on different dates after the intravenous injection of the standard dose of 4 mg. per kilogram may give a

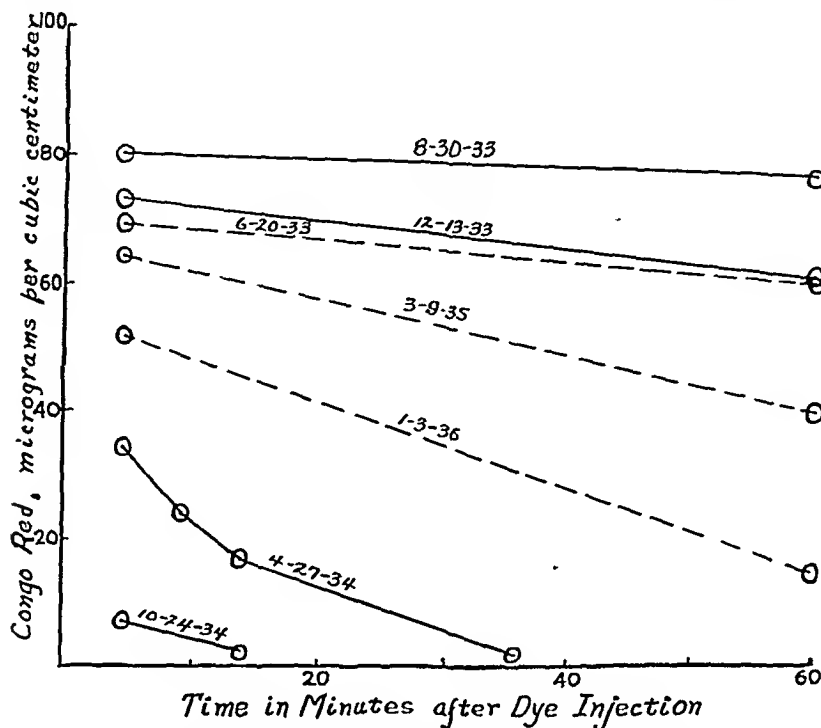


Fig. 1.—Acceleration in the rate of clearance of congo red from the blood stream with the accumulation of amyloid in 2 patients. The curves for each are designated by broken and by unbroken lines, respectively.

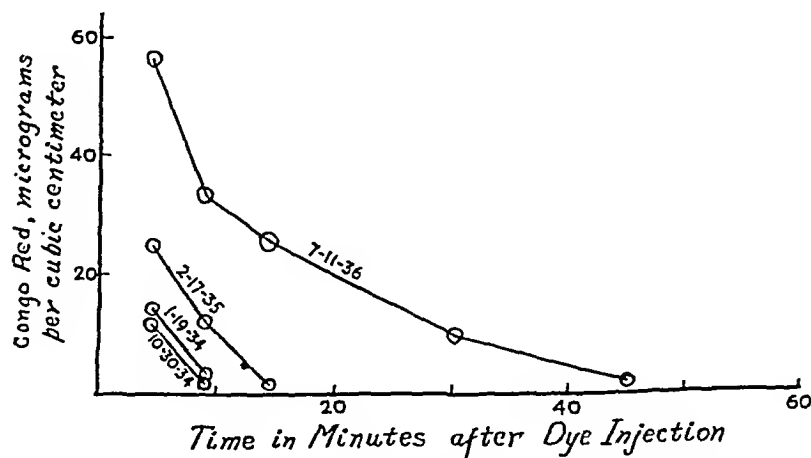


Fig. 2.—Deceleration in the rate of clearance of congo red from the blood stream with the disappearance of amyloid in 1 patient.

rough estimate as to whether the amount of amyloid present is increasing or decreasing (figs. 1 and 2). Determination of the disappearance time is done in the same way that quantitative determination of the total quantity of dye in oxalated blood

plasma is made except that withdrawal of specimens of blood is done every five minutes after the initial four minute specimen is obtained for a total of four specimens exclusive of the initial specimen. The time corresponding to the specimen

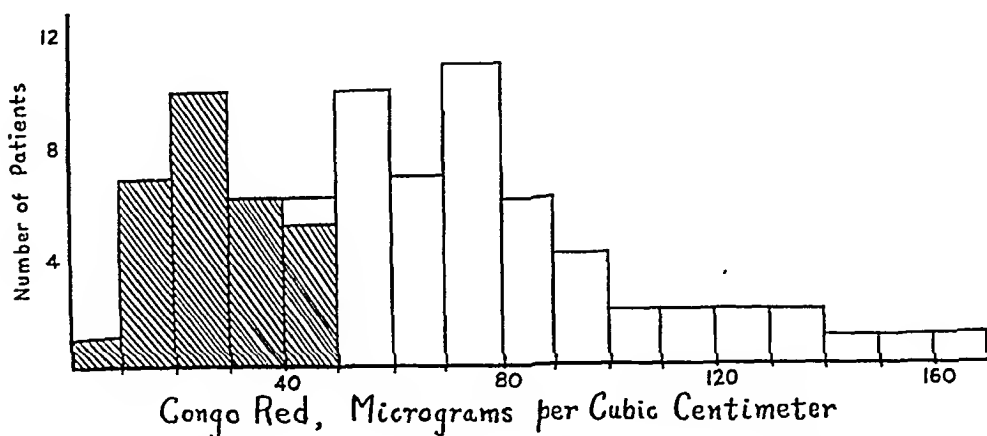


Fig. 3.—Concentration of congo red in the blood of persons with amyloid disease (shaded areas, twenty-nine determinations) and normal controls (unshaded areas, fifty determinations) four minutes after intravenous injection of the dye.

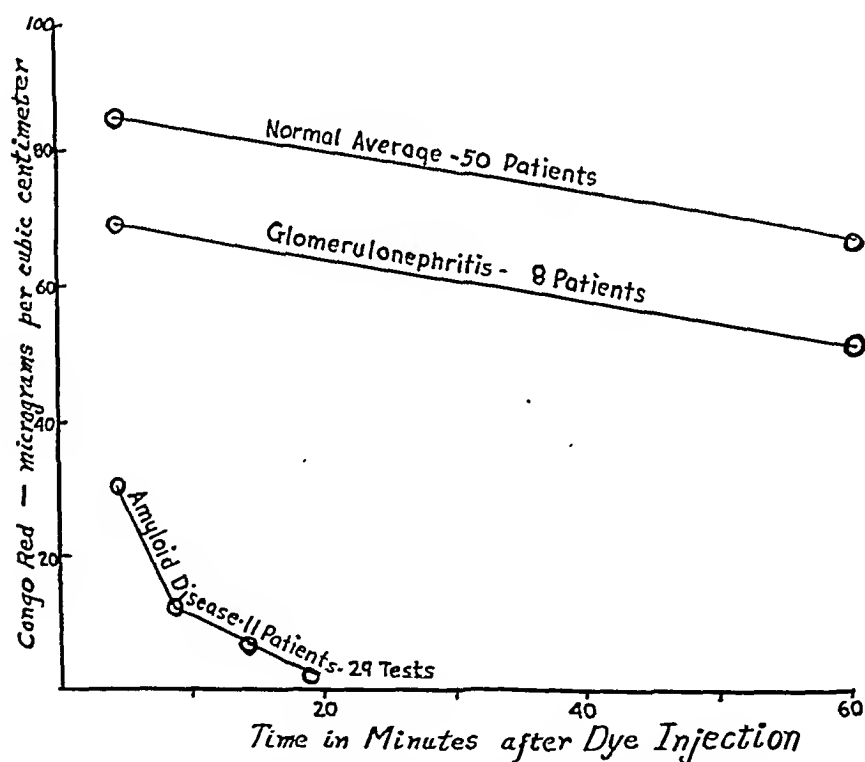


Fig. 4.—Average rate of disappearance of congo red from the blood stream in normal persons and in patients with glomerulonephritis and with amyloid disease.

in which the concentration of dye is so small that it cannot be estimated colorimetrically is designated as the time of disappearance.

Estimation of the dye in the urine is much less accurate than its estimation in blood plasma, as it is not possible to set up standards in urine that are comparable with the excreted product containing the dye. Production of a blue



color by acidification has not been any further aid. With care in handling the specimens of blood during collection and centrifugalization, we have not found it necessary to precipitate the proteins by alcohol or acetone, as advocated by Friedman and Auerbach and by Taran.

### RESULTS

This report is a summary of the results of one hundred and thirty-nine tests, 92 of which were performed according to the quantitative technic just described. The average level of congo red in the blood four minutes after intravenous injection was 85.7 micrograms per cubic centimeter in fifty determinations made on normal controls, 29.6 micrograms per cubic centimeter in twenty-nine determinations made on 11 patients with amyloid disease and 71.5 micrograms per cubic centimeter in eight determinations made on patients suffering from chronic glomerulonephritis. Figure 1 demonstrates the accumulation of appreciable stores of amyloid during the progression of the disease. Conversely (fig. 2), similar curves also will demonstrate deceleration of removal from the blood stream, a phenomenon which presumably parallels recovery and disappearance of amyloid deposits. This phenomenon has been discussed more freely in another paper,<sup>2</sup> dealing with the clinical phases and the diagnosis of amyloid disease. Figure 3 presents a graphic analysis of the initial levels of congo red attained in the blood in seventy-nine determinations on the normal persons and those with amyloidosis. The lower levels and the faster disappearance in persons with amyloid disease is related to the immediate absorption of the dye from the blood stream by deposits of this substance.

The average disappearance curves of the dye from the blood stream in three classes of patients as determined by our tests is given in figure 4. The average rate of disappearance in persons having amyloid disease is radically different from that in normal controls and from that in persons suffering from albuminuria due to chronic glomerulonephritis. The interpretation, utility and reliability of this test have been discussed in another paper.<sup>2</sup>

### SUMMARY

A quantitative technic for execution of the congo red test is described. Standards are given, and average disappearance curves and values for the level of congo red in the blood are presented.

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# UTILITY OF THE CONGO RED TEST IN DIAGNOSIS AND IN DIFFERENTIAL DIAGNOSIS

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During the past few years the congo red test for the confirmation of amyloid deposits in the body has been serviceable in our hands in elucidating the nature of obscure enlargements of the spleen and the liver. Since this test is not as well known as it deserves to be, and since we feel that many problems in diagnosis might be clarified by its use, reports are presented of 7 cases in which this test was of great value in arriving at a diagnosis. It should be emphasized that if positive, the information derived from the test is unequivocal, but there may be a small to moderate degree of amyloid present, undetectable by the test.

Bennhold<sup>1</sup> found that congo red, if carefully prepared, could be injected intravenously without danger. He presented 10 cases demonstrating that amyloid deposits in the liver would remove the dye rapidly from the circulating blood. This author also observed that patients with albuminuria due to noninflammatory disease of the kidney (nephrosis) eliminated quantities of the dye in the urine. There have been but a few additional reports<sup>2</sup> on the application of the method to a series of patients since the appearance of the original communication.

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From the Division of Orthopedic Surgery, Department of Surgery, the University of Chicago.

1. Bennhold, H.: Ueber die Beziehungen des Kongorotes zur amyloiden Substanz und über den Mechanismus der beschleunigten Farbstoffausscheidung bei tubulären Nierenkrankheiten, *Klin. Wchnschr.* **3**:1711, 1924; Ueber die Ausscheidung intravenös einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, *Deutsches Arch. f. klin. Med.* **142**:32, 1923.

2. (a) Bookman, A., and Rosenthal, J.: The Clinical Value of Intravenous Injection of Congo Red in the Diagnosis of Amyloid Disease, *Am. J. M. Sc.* **173**: 396, 1927. (b) Barker, N. W., and Snell, A. N.: The Congo Red Test with Special Reference to Excretion of the Dye in the Urine, *J. Lab. & Clin. Med.* **16**:262, 1930. (c) Shapiro, P. F.: Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis, *Arch. Int. Med.* **46**:137 (July) 1930. (d) Wallace, J.: Diagnosis of Amyloid Disease by the Intravenous Injection of Congo Red, *Lancet* **1**:391, 1932. (e) Rosenblatt, M.: The Clinical Manifestations of Amyloidosis, *Ann. Int. Med.* **8**:678, 1934; (f) Amyloidosis and Amyloid Nephrosis, *Am. J. M. Sc.* **186**:558, 1933. (g) Lipstein, S., and Auerbach, O.: An Evaluation of the Congo Red Test for Amyloidosis, *Quart. Bull., Sea View Hosp.* **2**:120, 1937.

Elsewhere<sup>3</sup> data from a series of tests have been analyzed. All previous authors have employed the original method of Bennhold, which consists merely of a comparison of the amount of the dye left in the blood stream at the end of one hour with that originally present just after injection.

#### METHOD

Bennhold injected either 10 cc. of a 1 per cent aqueous solution of congo red or 15 cc. of a 0.75 per cent solution intravenously. Four and sixty minutes after injection samples of blood were drawn, coagulation being prevented by coating tubes with paraffin. The two samples were then compared colorimetrically, and the percentage of dye left after sixty minutes was expressed in terms of the four minute specimen, which was used as a standard.

We have modified the test by injecting intravenously 4 mg. of congo red per kilogram of body weight as a 1 per cent solution. Specimens of blood are removed four and sixty minutes after injection. When the presence of amyloid disease is suspected and we wish to estimate roughly the amount of amyloid present, intermediate specimens are obtained.<sup>3</sup> For example, in the presence of a large quantity of amyloid, specimens drawn ten to fifteen minutes after injection of the dye usually do not show any trace of red or pink coloration. It is then desirable to repeat the test and determine the disappearance time of the dye from the peripheral blood stream. A detailed description of the technic can be found in another report.<sup>3</sup> The amount of the dye in micrograms per cubic centimeter of original blood plasma is obtained.

#### RESULTS

We have made one hundred and thirty-nine injections of congo red according to the technic just described in 69 different patients. Extreme and median values for the amount of congo red present in the circulating blood stream (oxalated plasma) after the intravenous injection of the standard amount are given in table 1. In accordance with the experiences of Bennhold<sup>1</sup> and others,<sup>2</sup> whenever a palpably enlarged spleen or liver has been produced by amyloid infiltration of that organ, the intravenous injection of congo red is followed by a rapid disappearance of the dye from the peripheral blood stream, thus leaving colorless the specimen of blood drawn after an hour. The interpretation of a partial clearance of the dye from the blood stream after an hour will be discussed later. We have preferred to make a clinical and laboratory diagnosis of amyloid disease only when the dye was completely removed from the blood after an hour; however, we have included as an illustration of a positive test a single case (8) in which there was 72.7 per cent absorption in an hour, since subsequent autopsy disclosed the presence of amyloid. Lipstein and Auerbach<sup>28</sup> investigated this question, having available 12 cases in which there was greater than 50 per cent absorption of the dye during life but in which there was no demon-

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3. Harmon, P. H., and Kernwein, G.: Congo Red Test for Amyloid Disease: A Quantitative Technic, *Arch. Int. Med.*, this issue, p. 416.

strable amyloid at necropsy. In only 1 of these cases was there complete absorption of the dye in one hour. Thus, if complete absorption is adopted as the standard of a "positive" test, rather than absorption of more than 50 per cent, as advocated by Bennhold, a positive congo red test will have great significance. In all (8) of our patients in whom complete clearance of the dye from the blood stream occurred in one hour and who subsequently came to autopsy amyloid was encountered in the organs in large quantities. The presence of amyloid in the liver, spleen and other organs was confirmed at necropsy in 10 of our patients. The test indicated large quantities of amyloid in 8 additional patients. Of this last-named group, 2 had a palpably enlarged liver at the time of the first examination and 2 appeared to be recovering from amyloid disease as judged from the results of the dye test, disappearance of albuminuria and anemia and improvement in general well-being. The

TABLE 1.—*Concentration of Congo Red After Intravenous Injection of Four Milligrams per Kilogram of Body Weight, Calculated as the Amount in Undiluted Blood Plasma (Micrograms per Cubic Centimeter)*

Clinical Status	No. of Patients	4 Min. After Injection			1 Hr. After Injection		
		Lowest	Highest	Median	Lowest	Highest	Median
History of chronic suppuration; no amyloid disease	38	49.1	128.3	75.0	24.4	106.5	55.0
Amyloid disease .....	11*	4.7	57.3	26.4	0	14.3	0
Acute and/or chronic glomerulonephritis	8	50.8	106.3	67.5	21.8	90.6	48.1

\* Twenty-nine tests on 11 patients.

remaining patients had appreciable amounts of amyloid deposits as judged by the dye test, but their livers and spleens were not palpable. In other instances the congo red test has enabled us either to dismiss the possibility of amyloid disease or to demonstrate the nature of an obscure enlargement of the liver or the spleen.

#### REPORT OF NINE CASES IN WHICH THE TEST WAS OF VALUE IN DIFFERENTIAL DIAGNOSIS

CASE 1.—A boy 9 years of age with a history of two years' disability from generalized juvenile atrophic arthritis (Still's disease) was first tested in April 1932. During fifteen months previously there had occurred four periods of several weeks when activity of many joints was present, with a daily exacerbation of temperature to 102.4 or 104 F. (39 or 40 C.). He had been treated by conservative orthopedic procedures aimed at prevention of deformity. Many repeated blood cultures remained sterile. During the early months of 1932 there appeared progressive enlargement of the liver, so that when we first saw the patient the liver was palpable 6 cm. below the right costal margin in the midclavicular line. Flaring costal margin and a protuberant abdomen were present. The patient was moderately anemic, the hemoglobin concentration (Sahli) being 60 per cent and the red

blood cells numbering 3,090,000 per cubic millimeter. The patient was excreting a large quantity of albumin in the urine, graded by the Heller nitric acid test as 4 plus. Only an occasional epithelial cast was found in the urine. No suppuration had been present at any time. Fifteen minutes after injection of 4 mg. per kilogram of congo red intravenously the dye all disappeared from the blood stream. None appeared in the urine. The diagnosis was amyloid disease involving the liver and kidneys, occurring as a complication of generalized juvenile atrophic arthritis (Still's disease).

CASE 2.—A boy aged 12 had a fifteen months' history of multiple chronic osteomyelitis involving the mandible, the left and the right femur, the left fourth metacarpal, the right tibia, the right scapula, the right fifth rib and the right humerus, with a pathologic fracture of the right femur. Liver dulness was increased to the right costal margin, but that organ was not palpable. The patient had severe secondary anemia, with a hemoglobin concentration of 45 per cent (Sahli) and a red cell count of 2,900,000 per cubic millimeter. There was no albuminuria. Four milligrams per kilogram of congo red was injected intravenously. The specimen of blood removed at the end of one hour showed the same amount of dye as that present four minutes after injection. Thus, regardless of the long history of severe and widespread suppuration and the severe anemia, the congo red test showed no amyloid to be present at this time. During the following nine months, osteotomies were done and two large soft tissue abscesses were drained. During a period of six weeks, the patient ran a low grade fever (temperatures of 99.5 to 100.5 F. [37.5 to 38 C.]) and a moderate amount of albumin appeared in the urine. The liver and the spleen were still not palpable. A repetition of the congo red test at this time demonstrated a total disappearance of the dye from the blood stream in twenty-five minutes. None appeared in the urine. Later tests showed a still more rapid disappearance of the dye from the blood stream. This patient was thus shown to have acquired amyloid disease of moderate severity while under hospital treatment for multiple chronic osteomyelitis. He subsequently died and was examined at necropsy.

CASE 3.—A 12 year old boy had had chronic osteomyelitis of the lower portion of the left tibia for fifteen months. The lesion had been healed for twelve months when a blow to the area was followed by an acute local recurrence of the infection. In addition to the local condition, we observed that the patient's urine contained much albumin and 20 to 30 red cells and 5 to 10 white cells per high power field of the microscope. These urinary changes had also been present on the patient's first admission but had rapidly subsided as the infection was brought under control. Examination of the blood showed that the patient was not anemic. At neither time was the liver or the spleen palpable. The congo red test, performed by the intravenous injection of 4 mg. per kilogram of the dye, showed that 71.8 micrograms per cubic centimeter (74 per cent of 86.3 micrograms per cubic centimeter, the amount present after four minutes) remained in the blood after one hour. None of the dye was excreted in the urine. Nine months after the first test the patient returned with another local recurrence of osteomyelitis, with similar urinary findings. The dye test was repeated, with similar results. The diagnosis was chronic glomerulonephritis and recurrent osteomyelitis.

CASE 4.—A man aged 50 had had a chronic cough following pneumonia for six years. During the six months just before we saw him the cough had been more productive and the sputum purulent. The patient had been weak, and there had been a loss in weight of 30 pounds (14 Kg.) during the previous year.

The physical examination showed among other things marked clubbing of fingers. The spleen and the liver were each palpable 6 cm. below the costal margin in the respective anterior axillary lines. There were a few coarse rales over the base of the chest. Examination of the blood showed a hemoglobin concentration of 52 per cent (Sahli) and a red cell count of 3,100,000 per cubic millimeter. The white cells numbered 6,000 per cubic millimeter. The urine showed appreciable albumin, graded from 2 plus to 4 plus, with a moderate number of epithelial casts and occasional white cells and red cells. Roentgenograms of the chest showed some soft disseminated infiltrative lesions in the lower portion of the chest on the right side, interpreted as bronchiectatic markings. The nonprotein nitrogen content of the blood was 118 and 84 mg. per hundred cubic centimeters on two observations, and the index of urea clearance was 5 and 9 (normal 40 to 65) on two different tests. The congo red test (4 mg. per kilogram of body weight) showed 90 per cent retention of the dye in the blood stream after one hour. None appeared in the urine. The final diagnosis was chronic glomerulonephritis with nitrogen retention, chronic bronchiectasis, secondary anemia and cardiac decompensation, with chronic passive congestion of the liver, spleen and kidneys.

CASE 5.—The patient was a woman aged 32. Infection had occurred at another hospital after an open operation for bilaterally fractured patellas. This was followed by unilateral pyoarthrosis and almost complete fibrous ankylosis of the same knee. When the patient was seen by Dr. D. B. Phemister, fourteen weeks after the infection had occurred, there was still a draining sinus present and some swelling and tenderness about the knee, with only 5 degrees or less of passive motion possible. The patient was having a persistent afternoon temperature, ranging between 100.5 and 102 F. (38 to 38.8 C.). The spleen was palpable 3 cm. below the left costal margin in the anterior axillary line. The liver was not palpable. The patient had a moderate degree of secondary anemia, with a hemoglobin concentration of 65 per cent and a red cell count of 3,550,000 per cubic millimeter. The congo red test, done by the injection of 4 mg. per kilogram intravenously, showed 66.9 micrograms of the dye per cubic centimeter to be present in the blood stream at the end of an hour (85 per cent of 75 micrograms per cubic centimeter, the amount present after four minutes). None was excreted in the urine. The dye test indicated that amyloid was not present in this patient at this time.

CASE 6.—A man 65 years of age complained of dysphagia for solid food and of a sensation of a foreign body present in the lower part of the throat for seven weeks prior to seeking medical advice. He had lost 41 pounds (19 Kg.) in weight during the previous four months. On physical examination the patient showed general emaciation and cachexia. Other results of examination were not remarkable except for the enlargement of the liver to a point 10 cm. below the costal margin in the right midclavicular line. The edge of this organ was firm and rounded. A trace of albumin was present in the urine. Red cells numbered 4,070,000 per cubic millimeter. Roentgen examination with the aid of an opaque contrast medium administered by mouth demonstrated a lesion in the upper portion of the esophagus opposite the second to the sixth thoracic vertebra. Biopsy of material obtained through an esophagoscope revealed an epidermoid carcinoma. The congo red test was made by the intravenous injection of 4 mg. per kilogram of body weight. There was 61.3 micrograms of dye per cubic centimeter (82 per cent of 74.4 micrograms per cubic centimeter, the amount present after four minutes) remaining in the patient's blood stream after one hour. None appeared in the urine. The diagnosis prior to operation was carcinomatous stenosis of the esophagus. The cause

of the enlarged liver was not definitely decided, except that it was not due to the deposition of amyloid. At an abdominal exploration, at which time a gastrotomy was also done, a firm and finely nodular liver, typical of alcoholic cirrhosis, was encountered. The patient's immediate postoperative course was excellent, as he was soon able to take fluids and food through the gastrotomy opening. During the course of subsequent high voltage roentgen therapy, the patient lost more weight and strength, an intractable cough developed and the patient finally died. At necropsy amyloid was not present in the enlarged liver.

CASE 7.—A boy 6 years of age presented himself with draining sinuses in the left arm and left leg. He was obviously anemic, underweight and malnourished. The onset had been ushered in with chills and fever following trauma, the patient having been treated for "malaria" before a definite diagnosis was established. Swelling of the scrotum and the abdomen had occurred during the course of the acute illness, and fluid had accumulated in the chest, necessitating aspiration of the chest six times in the four months before the patient was seen at the University of Chicago Clinics. On admission he had edema of the eyelids. On the left side, the superficial veins of the neck were distended and there was a venous pattern on the anterior aspect of the chest. Dulness and diminished breath sounds were present in the chest on the left side. The spleen was palpable 8 cm. below the right costal margin in the left nipple line. The upper portion of the left humerus was palpably enlarged, and three healed scars were present. There were two discharging sinuses over the left tibia. Examination of the blood showed the red cell count to be 5,040,000 per cubic millimeter, the white cell count 10,600 per cubic millimeter and the hemoglobin concentration 80 per cent. Albumin (1 plus) was present in the urine. Roentgenograms showed a massive pleural effusion on the left side, which on aspiration yielded seropurulent fluid. Changes characteristic of chronic osteomyelitis were seen in the left tibia and the left humerus. The congo red test showed 64 micrograms per cubic centimeter in the blood stream at the end of one hour (80 per cent of 80 micrograms, the amount of the blood four minutes after injection). The diagnosis was chronic (left) thoracic empyema and chronic pyogenic osteomyelitis of the left tibia and the left humerus. It was thought that the patient did not have amyloid disease because of the rapid disappearance of the splenic enlargement in conjunction with the negative dye test. His subsequent course proved this to be correct.

CASE 8.—A girl aged 11, a sister of the patient in case 7, presented herself with multiple chronic rheumatoid arthritis (Still's disease) of three years' duration. On entrance and intermittently for the ensuing four years of observation, she presented mild to moderate edema of the face and eyelids, associated with slight to moderate intermittent albuminuria. During three of these four years the patient remained in good general condition, but during the fourth year she began to lose weight, became cachectic and finally died in a coma associated with nitrogen retention. Never at any time was either the liver or the spleen palpable. The congo red test done on two occasions during the first two years of observation showed 88 and 60 per cent retention in the blood stream, but a third test done a few months prior to death showed a blood level of 14.3 micrograms per cubic centimeter at the end of one hour (27.3 per cent of the level of 52.3 micrograms per cubic centimeter four minutes after injection). At necropsy a moderate degree of generalized amyloidosis was found, especially in the kidneys.

CASE 9.—A boy aged 15 years had a tibial leg-lengthening osteotomy performed. For four successive days the color of the lower portion of the leg remained

cyanotic and the temperature elevated. On the fifth and the sixth day definite gangrene of the leg appeared. A pure culture of  $\beta$  hemolytic streptococci was isolated from the wound and from around the pin holes. A mid thigh amputation was performed in an attempt to save the patient's life, but he died ten hours after the amputation. Two years before the first surgical procedure it had been observed that he had a trace of albumin in the urine. At that time a congo red test, done because of the history of chronic suppuration, showed that 80 per cent of the dye remained in the blood plasma at the end of an hour. In the ensuing two years the albumin disappeared from the urine. A second congo red test performed the day before death showed 79 per cent of the dye in the blood stream at the end of an hour (initial level after four minutes being 53.4 micrograms per cubic centimeter). The necropsy showed moderate to advanced amyloid infiltration in the glomeruli and slight amyloid infiltration in the liver, spleen and adrenal glands. The septic thrombosis of both renal arteries observed post mortem may have been responsible for the negative dye test on the latter occasion.

#### DIFFERENTIATION OF NEPHRITIDES BY THE CONGO RED TEST

In Bennhold's report<sup>1</sup> on the use of congo red in the diagnosis of amyloid disease the possibility of utilizing this test to differentiate the types of nephritides was minimized. Since that time, however, there have appeared indications<sup>4</sup> that this dye might be employed in clinical laboratory tests to differentiate chronic glomerulonephritis from nephrosis. The difficulty of segregating certain stages of chronic glomerulonephritis (for example, the nephrotic stage) from pure nephrosis either by clinical appearance or by chemical examination of blood or urine is well known.<sup>5</sup> In an attempt to confirm and clarify the possible utility of the congo red test in this situation the tests summarized in table 2 were carried out. We attempted to correlate the urinary excretion of congo red in 7 patients with various stages and types of chronic nephritis and in 1 patient with orthostatic albuminuria with the amount of protein excreted in the urine during the period of examination. The clinical status of these patients, together with the data compiled in this study, is given in the accompanying table 2. Determinations of the dye were made colorimetrically both in blood plasma and in urine by comparison with standards. The amount found in the urine is an approximation as standards cannot be accurately proposed with urine as a diluent.

It can be seen by reference to table 2 that there was a wide variance between the amount of the dye excreted in the urine after the intra-

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4. Nathan, M.: Ueber die klinische Diagnose des Amyloidose mittels Kongorotinjektionen, München. med. Wchnschr. **75**:1883, 1928. Strasser, U.: Die Kongorotprobe auf Amyloid bei nephrotischen Symptomencomplex, Med. Klin. **25**:468, 1929. Shapiro.<sup>2c</sup>

5. Leiter, L.: Nephrosis, Medicine **10**:135, 1931. McClure, W. B.; de Takáts, C. B., and Hinman, W. F.: Mechanism of Edema of the Renal Type, Arch. Int. Med. **51**:819 (June) 1933.



TABLE 2.—*Relation of Proteinuria to Urinary Excretion of Congo Red*

Patient Number	Age of Patient, Years	Diagnosis	Clinical Edema	Total Plasma Proteins, Gm./100 Cc.	Hemoglobin, per Cent (Sahli)	Index of Urea Clearance, (Normal 40=65)	Congo Red		Urinary Excretion	
							Amount in Blood After 1 Hour in Micrograms 1 Cc.	Total Amount Excreted in Urine in 1 Hour, Micrograms	Cc. in 1 Hour	Total Protein in Sample, Gm.
10.....	28	Acute glomerulonephritis (recovery stage)	0	6.4	80	37	51.2 (66%)	Trace	90	0.518
11.....	56	Chronic glomerulonephritis	+	3.9	58	27	50.0 (80%)	1,520	65	1.491
12.....	61	Cardiorenal disease; generalized arteriosclerosis	0	7.2	80	10	90.6 (84%)	662	53	2.534
13.....	16	Acute glomerulonephritis (nephrotic stage)	+	3.6	70	56	21.9 (34%)	0	80	1.964
14.....	54	Chronic glomerulonephritis, with acute exacerbation; hypertensive cardiorenal disease	0	6.1	70	5	48.1 (69%)	Trace	87	0.897
15.....	14	Chronic glomerulonephritis (nephrotic stage)	+	4.7	85	Phenolsulfonphthalein excretion, 60% in 2 hours	24.4 (45%)	950	35	0.221
16.....	32	Chronic glomerulonephritis	0	5.5	60	6	45.7 (68%)	400	40	0.548
17.....	19	Orthostatic albuminuria	0	.....	95	....	31.3 (72%)	Trace	47	0.019

venous injection of a standard dose of congo red (4 mg. per kilogram of body weight) and the quantity of protein excreted in the urine during the same period. Further, there was no relation between the level of protein in the circulating blood, the presence of edema clinically, the functional efficiency of the kidney as measured by the index of urea clearance and either the amount of protein in the urine or the amount of congo red excreted in the urine. Normally, in human beings in the absence both of albuminuria and of amyloid deposits in the body, no congo red or a bare trace is excreted in the urine.<sup>6</sup>

#### COMMENT

The cases presented in this paper demonstrate the value of the congo red test in confirming the clinical impression of amyloid disease and for further clarification of the nature of obscure enlargements of the liver and the spleen. If a positive result, by which we mean complete removal of a standard dose of 4 mg. per kilogram of dye given intravenously, is obtained, there is little likelihood that the condition is other than amyloid disease. Only 1 case (reported by Lipstein and Auerbach) of a "false positive" test is on record if the criterion just mentioned is accepted. There was no explanation given for this singular result. In all of our severely ill patients, in whom complete absorption of the dye was present and who came to necropsy, the presence of amyloid deposits was demonstrable.

When the patients demonstrating only partial absorption of the dye are considered, especially that group in whom 50 to 90 per cent of the dye was removed from the blood stream, there is opportunity for misinterpretation of the result. The criterion originally established by Bennhold for a "positive" test needs modification and more liberal interpretation. It is our opinion that a partial absorption result should be considered as only "suggestive" of the presence of amyloid. Eleven cases were reported by Lipstein and Auerbach in which autopsies failed to yield evidence of amyloid deposits but in which during life more than 50 per cent absorption of the dye has been demonstrated. The tests in 3 of our patients fell into this category. One patient, with Still's disease and 72 per cent absorption, subsequently died, and changes typical of amyloid disease were encountered at necropsy. The other 2 patients are still well, with 51 and 60 per cent disappearance of dye. One of the patients is without any of the suggestive signs of amyloid disease except slight anemia (70 per cent hemoglobin) and intermittent slight albuminuria; in the other an accelerated and typical dye absorption curve later developed, but the patient recovered completely, with reversal of the dye absorption test.

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6. Bennhold.<sup>1</sup> Footnote 2.

False negative results may occur and should be interpreted with some caution, especially when other signs point to amyloid disease. In our series 1 patient had a negative test, interpreted according to the first-mentioned criterion (less than 50 per cent absorption). An autopsy was subsequently done, with the finding of amyloid in the organs. Lipstein and Auerbach also reported that in 1 patient in whom changes typical of amyloid disease were observed at autopsy only 35 per cent of the dye was absorbed. In our patient just mentioned thrombosis of the renal arteries was encountered at autopsy, and since the majority of the amyloid was in the kidney, that condition might have accounted for the false negative result. We had 1 patient in whom there was incomplete absorption (72 per cent), while Lipstein and Auerbach described 4 patients (3 showed 90 per cent absorption, and 1 had 95 per cent absorption), all having amyloid demonstrable at autopsy.

The question of recovery from typical amyloid disease associated with complete absorption of the dye can be answered in the affirmative. We have had 2 patients in whom complete reversal of the dye test occurred and a third who remained in excellent health and without anemia or albuminuria for five years. The result of the dye test in the third patient remained positive. In our opinion the 6 "recovered cases" reported by Grayzel and Jacobi<sup>7</sup> should be reduced to 2, inasmuch as the other 4 were probably in a period of spontaneous remission, since they still showed appreciable absorption of the dye and albuminuria. The same is true of the cases reported by Whitbeck.<sup>8</sup> Spontaneous remissions are common in this disorder, when for periods of several months the size of the viscera recedes, the patient gains weight, anemia improves and albuminuria disappears, but the congo red test remains positive. The criterion for recovery in the cases reported by Waldenström<sup>9</sup> was absence of amyloid in biopsy specimens obtained by liver puncture.

Our 2 instances of recovery bring the total number of recoveries from this disease reported in the literature to 11. Four instances were reported by Waldenström.<sup>9</sup> Two recoveries were described by Pearlman,<sup>10</sup> in addition to 2 cases in which regression occurred. In these

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7. Grayzel, H. G., and Jacobi, M.: Secondary Amyloidosis: Results of Therapy with Desiccated Whole Liver Powder, *Ann. Int. Med.* **12**:39, 1938.

8. Whitbeck, B. H.: Liver Meal in the Treatment of Amyloidosis, *J. Bone & Joint Surg.* **14**:85, 1932.

9. Waldenström, H.: On the Formation and Disappearance of Amyloid in Man, *Acta chir. Scandinav.* **63**:479, 1928; Ueber das Entstehen und Verschwinden des Amyloids beim Menschen, *Klin. Wchnschr.* **6**:2235, 1927.

10. Pearlman, A. W.: Regression of Amyloidosis, *Quart. Bull., Sea View Hosp.* **6**:92, 1940.

2 cases the interpretation of the dye test was questionable, as there was incomplete elimination of the dye from the blood stream. Habein,<sup>11</sup> Rosenblatt<sup>12</sup> and Reimann<sup>13</sup> each reported an instance of recovery in which there was complete reversal of the dye test. Prior to the introduction of the congo red test 4 instances of recovery<sup>14</sup> were recorded, but these recoveries, while suggestive, must remain conjectural, as they cannot be confirmed by modern rigid criteria. It is difficult to estimate the percentage of recovery in cases of this disease, as the reports are in the main of single cases. Judging from our series and those of Waldenström, Grayzel and Jacobi and Pearlman, "permanent" recoveries with reversal of the dye test occur in less than 10 per cent of cases, even when suppuration has been minimized. Elimination of suppurative foci appears to be the only reliable basic means of controlling the disease. Since the complication occurs most frequently in persons with cavernous pulmonary tuberculosis, with secondary infection associated with tuberculous joint disease and with chronic multiple pyogenic osteomyelitis, the difficulty results from unsatisfactory treatment of or response to the original disease. Encouraging results in treatment have been reported with desiccated liver meal by Whitbeck and by Grayzel and Jacobi. However, the use of this material must be considered as an adjuvant to elimination or control of suppuration, inasmuch as the results reported by these authors were not uniformly successful. We treated 4 patients with liver meal for almost a year without observing more benefit than regression similar to that occurring under favorable conditions without this treatment. Periods of "spontaneous" regression in the disease must be fairly common, since they occurred one or more times in 10 of our 11 patients. A regression simulates a "recovery" closely but is distinguished from it by the temporary duration of the regressive phase and failure of the congo red test to reverse during the episode.

It should be pointed out that although suppuration is the most common associated or causative condition in the production of amyloid disease, it is not necessary always to have suppuration as a preliminary condition. It is a common complication of Still's disease (2 instances in our series) and of multiple myeloma.<sup>15</sup> The common association of

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11. Habein, H. C.: Amyloidosis: Report of a Case in Which the Patient Recovered, Proc. Staff Meet., Mayo Clin. **9**:261, 1934.

12. Rosenblatt, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis, Arch. Int. Med. **57**:562 (March) 1936.

13. Reimann, H. A.: Recovery from Amyloidosis, J. A. M. A. **104**:1070 (March 30) 1935.

14. Gardner, W., cited by Pearlman.<sup>10</sup> Kretzschmar, P. H., and Westbrook, B. P., cited by Pearlman.<sup>10</sup> Owen, I., cited by Pearlman.<sup>10</sup> Walker, G. F., cited by Pearlman.<sup>10</sup>

15. Rosenblum, A. H., and Kirshbaum, J. D.: Multiple Myelomas with Tumor-Like Amyloidosis, J. A. M. A. **106**:988 (March 21) 1936.

the disorder with suppuration and the relative hopelessness of ultimate prognosis in a patient in whom the diagnosis of amyloid disease has been established, argues strongly in favor of a periodic check-up by means of the congo red test of persons in whom the control of suppuration by the recognized conservative surgical methods has been imperfect. It further suggests the more common employment of amputation and bone resection when conservative surgical means have not sufficed to bring chronic bone suppuration under control. The employment of these more radical measures within a few weeks or months of the establishment of a positive dye test in instances of single uncontrollable suppurative foci would be a life-saving measure. In retrospect, 1 of our patients likely would not have died had we been successful in obtaining permission to perform a hip joint disarticulation two years prior to the date on which it was finally performed.

Serial and periodic examination by the congo red test of persons harboring a suppurative focus yields valuable data on the minimal time required after the onset of suppuration for enough amyloid to develop to give a positive congo red test. The authorities previously cited (Waldenström, Lipstein and Auerbach and Whitbeck) expressed the belief that one to two years are required after the onset of suppuration until "amyloid disease develops." The data on 9 of our patients are sufficient to fix within a span of a few months the accumulation of sufficient amyloid to give a positive dye test. This period from onset of suppuration (or arthritis in 2 patients with Still's disease) was nine months for a 5 year old child, one and a half years for 2 patients, two years for 3 patients, four years for 2 patients and eight years for 1 patient. It is possible that age may be a factor of relative resistance to amyloid disease, but we do not have sufficient data either to prove or to disprove this contention.

#### CONCLUSIONS

1. The congo red test is valuable as an aid in differential diagnosis of obscure swellings of the liver and the spleen.

2. When the test is positive (rapid disappearance of the dye from the circulating blood plasma within a few minutes), a diagnosis of amyloidosis can be made.

3. The test gives no clue to the distribution of the amyloid deposits in the body.

4. Slight to moderate amounts of amyloid may be present, and the test will fail to reveal this fact (2 illustrative cases are reported). A negative test is not positive proof that amyloid is not present, but when taken in conjunction with other data it may point to that conclusion.

5. The test is of no value in distinguishing between the stages of chronic glomerulonephritis or nephrosis or between these two states

and orthostatic albuminuria, although the dye is excreted in the urine in large quantities when albuminuria is present in the absence of amyloidosis.

6. Methods of determining blood volume using congo red are invalid in the presence of amyloidosis or albuminuria from any cause.

7. The congo red test is valuable in following the course of patients with amyloid disease and is of some prognostic value. In recovery from this disease the positive dye test is the last sign to disappear, this occurring some months after disappearance of palpable organs, anemia and albuminuria.

8. The minimum time for the accumulation of sufficient amyloid to give a positive dye test is nine months, and the average is one and one-half to two years.

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# HODGKIN'S DISEASE WITH SPECIFIC LESIONS APPEARING FIRST IN THE SKIN

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PHILADELPHIA

In cases of chronic lymphogranulomatous disease, particularly when the gross or the histologic lesions accessible for examination are not pathognostic of any one recognized entity, both clinical and histologic diagnoses may be confused. This is especially true in cases of Hodgkin's disease when it is unusual in character. In some cases of atypical disease the diagnosis may be made because no other classification is possible in the light of present knowledge, and in others, as in the one reported here, it may be mistaken for other diseases. The final diagnosis is often established at necropsy, when all available data are at hand.

In the present case Hodgkin's disease was suspected early in the course, but because of the unusual onset with the earliest and most prominent lesions in the skin and the absence of demonstrable enlarged lymph nodes and later because of the histologic changes in excised bits of tissue from the skin, lung, spleen and bone marrow, the possibility of chronic, relapsing, febrile, nonsuppurative panniculitis arose. This syndrome, also known as Weber-Christian disease, of which about 20 cases have been recorded, seems to be almost as rare as cases of Hodgkin's disease in which the first specific lesions appear in the skin. It is of unknown causation; occurs mostly in women; is characterized by multiple inflammatory nodules in the panniculus adiposus, which heal with atrophy to leave depressions in the skin, and like Hodgkin's disease, is relapsing in type with prolonged irregular, intermittent fever. In our case the condition conforms with this definition except for the visceral involvement, the occurrence in a man, the occasional ulceration of a cutaneous lesion and the fatal end. So far as the cutaneous lesions are concerned, it was indeed a case of panniculitis but with grave systemic involvement as well, all a part of the chronic granulomatous condition called Hodgkin's disease.

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From the Department of Medicine and the Clinical Laboratory, Jefferson Medical College Hospital.

Presented at the meeting of the Association of American Physicians, Atlantic City, N. J., May 6, 1941, as a report of a possible case of relapsing, febrile, nodular panniculitis.

## REPORT OF A CASE

In March 1939 R. B., a machinist aged 45, tired more easily than usual. In April several "fiery red" spots which were about 5 mm. in diameter, itched and at times were painful enough to keep him awake at night appeared on the extensor surface of the right arm near the elbow. After several days the spots gradually faded and left pigmented areas. He continued to work but lost weight, strength and appetite. Three weeks later, similar but more numerous and less painful nodules appeared on the abdomen and chest. Most of these subsided after several weeks and left brownish spots. Some of them ulcerated and were covered with dark brown crusts. These healed slowly and left deep depressions, which slowly filled in until they were nearly level with the surrounding skin. In May he entered a hospital with jaundice, and pitting edema of the ankles, scrotum and skin up to the xiphoid process developed and lasted five weeks. During the next five weeks more spots developed on his legs, without itching or pain. There was a remittent fever, the highest temperatures reaching 39.5 C (103 F.) on several occasions but usually rising to 38.3 C. (101 F.). The inguinal and the axillary lymph nodes were noted as palpable at this time, but otherwise extensive study failed to reveal the cause or the nature of the patient's illness until an excised lesion was examined histologically by a dermatologist, who suggested a diagnosis of panniculitis or Weber-Christian disease.

Laboratory studies of the blood in June revealed 75 per cent hemoglobin, 4,000,000 erythrocytes and 6,000 leukocytes per cubic millimeter and a sedimentation rate of 10 mm. in one hour. A roentgenogram of the chest made in June showed increased density of the tracheobronchial shadows and broadening of the peripheral bronchi as well, suggestive of an infiltrative process.

As too often happens in diseases of unknown origin, the patient's tonsils were suspected as a cause and excised. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was also given, without beneficial effect.

The patient improved for a time at home but was still febrile. The cutaneous lesions subsided. Several weeks later he became worse with high fever and reentered the hospital on September 1. At this time the eruption on the skin reappeared in its most active stage (fig. 1). The spleen was now palpable, and a roentgenogram of the chest showed enlargement and intensification of the hilar shadows and bronchial markings extending to the lower lobe of the right lung resembling the changes seen in pulmonary Hodgkin's disease. The hemoglobin concentration dropped to 65 per cent and the erythrocyte count to 3,000,000. The leukocytes numbered 1,200, of which 69 per cent were polymorphonuclear cells, 20 per cent small lymphocytes and 11 per cent monocytes. The sedimentation rate was 34 mm. in one hour. The patient was then sent to us for further study.

His complaints on entering Jefferson Medical College Hospital in September under our observation were sores on the skin, weakness, intermittent fever, headache and loss of 22.7 Kg. (50 pounds) of weight in seven months.

*Physical Examination.*—Except for evidence of loss of weight the patient did not seem to be seriously sick. The epitrochlear, the axillary and the inguinal lymph nodes were palpable but not significantly enlarged. The heart and lungs were normal, but the spleen and liver were both enlarged, firm and palpable. There was a faint erythematous eruption about the eyelids and chin, and numerous reddish brown macules of varying shades about 1 to 2 cm. in diameter, mostly about the size of a dime, and some of them depressed occurred on the arms, back, buttocks, abdomen and legs. Several had ulcerated and were covered with





Fig. 1.—Cutaneous lesions at the height of the eruption in the sixth month after onset. Several nodules have ulcerated. Dr. R. P. Batchelor, Palmerton, Pa., permitted us to use this photograph.

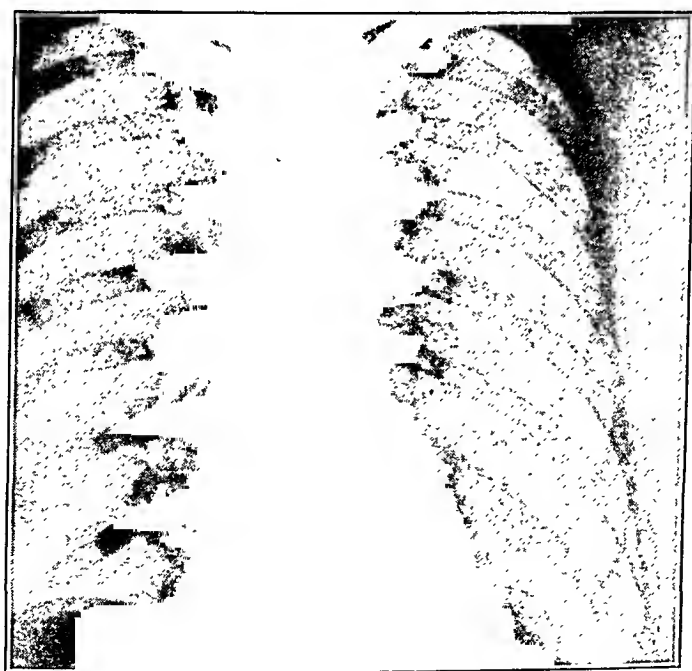


Fig. 2.—Roentgenogram made six months after onset. Note the rounded densities in the lower halves of both pulmonary fields suggestive of metastatic neoplasms. The hilar area is broadened as if by enlarged mediastinal lymph nodes.

black crusts. One deep crust-covered ulcer 5 mm. in diameter was present on the nasal septum. There was an area of brown pigmentation on the left side of the soft palate, but it was impossible to tell whether this was the remains of a lesion. New lesions occasionally appeared as pea-sized, firm, sometimes bright red, tender nodules. A few of the lesions persisted for several months and eventually became necrotic and dry and formed deep ulcers with sharp crater-like edges usually covered with a dark brown or black scab. Healed lesions usually left a yellowish brown discoloration; occasionally, it was permanent and the lesions were slightly depressed or level with the surface of the skin, but usually they left

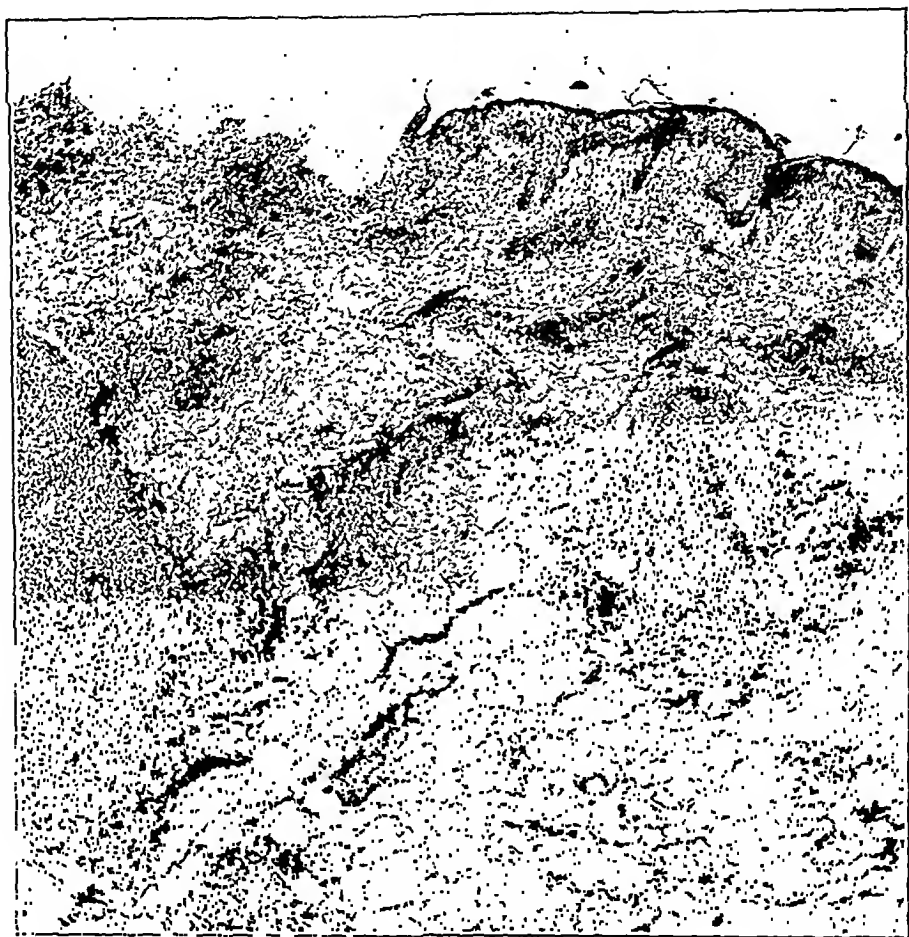


Fig. 3.—Skin and subcutaneous tissue ( $\times 37.5$ ). Collections of mononuclear cells are present in the derma and in the connective tissue, replacing the fat. The lesions deeper in the panniculus adiposus were much larger. The absence of epidermis in the upper left hand part of the section is an artefact.

no trace at all. It was estimated that more than one half of the total area of skin of the ventral surface of the body and one quarter of that of the dorsal surface had been involved in several relapses since the disease began. The face except for the erythema mentioned, the genitalia, the hands and the feet were free.

There were no physical abnormalities in the chest, but a slight cough which started in July persisted for several weeks. A second roentgenogram made in September (fig. 2), two weeks after the first one, showed round densities in the lower halves of both pulmonary fields, suggestive of metastatic neoplasms, and multiple areas of radiolucency resembling areas of emphysema. The hilar shadows

were broadened, indicating enlargement of the mediastinal lymph nodes. Another roentgenogram of the chest made in October showed general clearing since September, but several new opacities had developed.

*Laboratory Data.*—Numerous examinations of the blood showed an average of 3,500,000 erythrocytes, 65 per cent hemoglobin and 2,400 to 4,500 leukocytes, of which the granulocytes usually composed about 80 per cent. The platelets

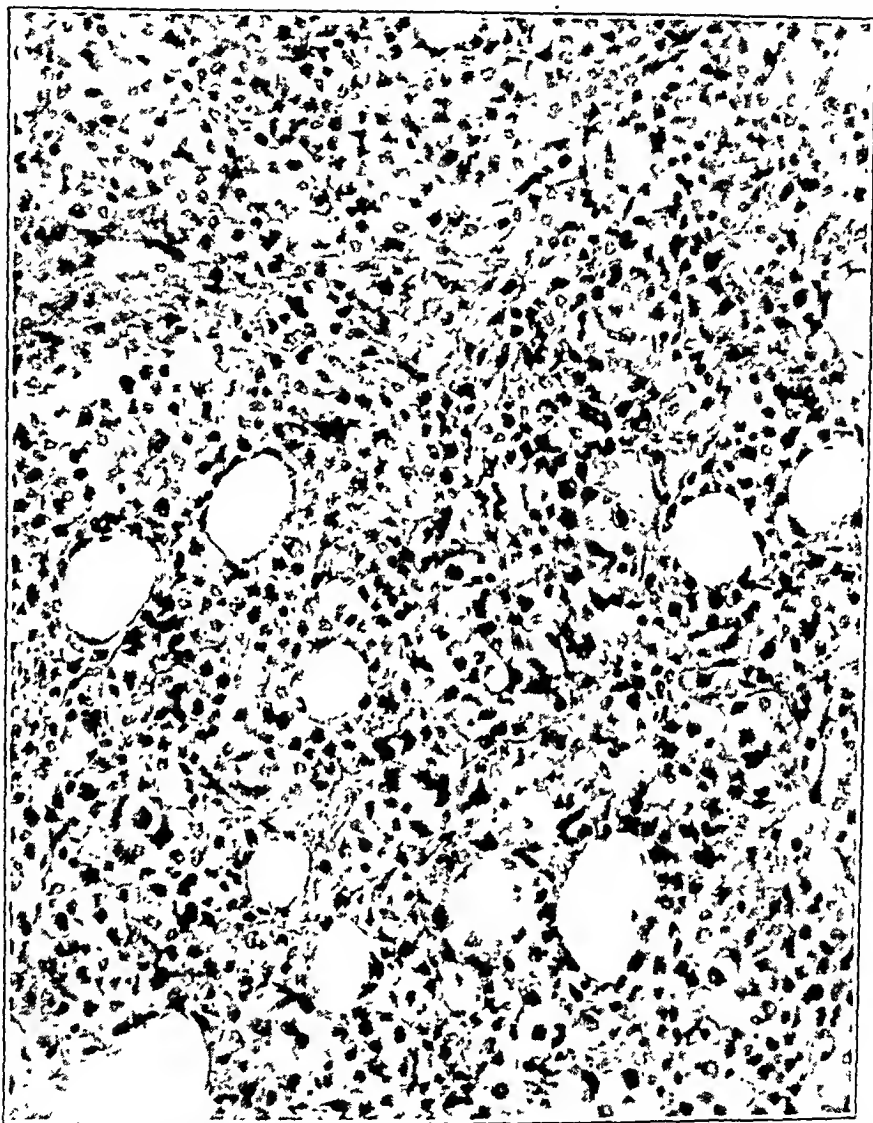


Fig. 4.—Lesions composed chiefly of lymphocytes, plasma cells and mononuclear cells of the Reed-Sternberg type in the panniculus adiposus ( $\times 335$ ).

averaged 190,000 per cubic millimeter. The sedimentation rate was 20 mm. in one hour. The urine was normal; blood cultures, cultures of the tissue removed at biopsy and Wassermann and Kahn reactions gave negative results. The prothrombin was 100 per cent of normal; the result of the direct van den Bergh reaction was positive and that of the quantitative reactions, 1.5 mg.; bromsulphalein injected intravenously was removed from the blood; the urine gave a positive reaction for urobilinogen in a dilution of 1 to 40, and bile pigment was absent

from the urine. The proteins of the blood measured 6.91 mg., of which 3.93 mg. was albumin and 2.98 mg. was globulin. Study of the cells from the bone marrow of the sternum showed hyperplasia of normal leukopoietic tissue.

A new cutaneous lesion and an old one were excised for study. There were no pathologic changes in the epidermis, but in the derma, in the connective tissue and to a greater extent in the subcutaneous fat patchy or nodular, nonspecific inflammatory lesions more or less granulomatous in character replaced the fat (fig. 3). In the derma the lesions collected around small blood vessels sebaceous glands and sweat glands. In the subcutaneous tissue (fig. 4) the lesions were composed of fairly extensive, scattered, but not sharply delineated collections of cells, with edema and areas of necrosis. The cells were mostly lymphocytes, with a few plasma cells and rare polynuclear giant cells. The latter were not a conspicuous part of the picture. No lipolytic macrophages were seen, nor were there



Fig. 5.—Roentgenogram made eight months after onset. As compared with figure 2, it shows a generalized increase in the pulmonary markings, with diffusely scattered flocculent or mottled densities in both pulmonary fields. The nodular densities have faded somewhat.

thrombi or evidence of endarteritis in the small blood vessels in the involved areas. The chief difference between the young and the old lesions was the greater diffusion and the presence of a greater degree of necrosis in the latter. The lesions conformed generally with those described in cases of panniculitis.<sup>1</sup>

The patient was observed at intervals during the next nineteen months. He was weak and failed to regain weight. Isolated nodules appeared in the skin from time to time, coincident with periods of low fever. The spleen and the liver remained palpable and firm. Leukopenia (2,000 to 3,000 cells) and moderate

1. Bailey, R. J.: Relapsing, Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), *J. A. M. A.* **109**:1419-1424 (Oct. 30) 1937.

secondary anemia persisted. Tissue taken from the sternal marrow in July 1940 showed hyperplasia and many mononucleated young megakaryocytes. There were occasional slight cough and a surprising absence of abnormal physical signs in spite of the ever changing massive nodular shadows revealed by roentgen examination. These shadows waxed and waned independently of the dermal eruption. Roentgenograms made at intervals are shown in figures 5 and 6.

In January 1941 a pulmonary nodule shown in figure 6 was aspirated. The histologic nature of the tissue was similar to that of the cutaneous lesions (fig. 4) and is shown in figure 7. Heavy exposure of the left lung to roentgen rays failed to cause any change in the size of the nodules.

During the next few months the patient gradually failed; he died at his home in May 1941, about two years after the onset of his illness.

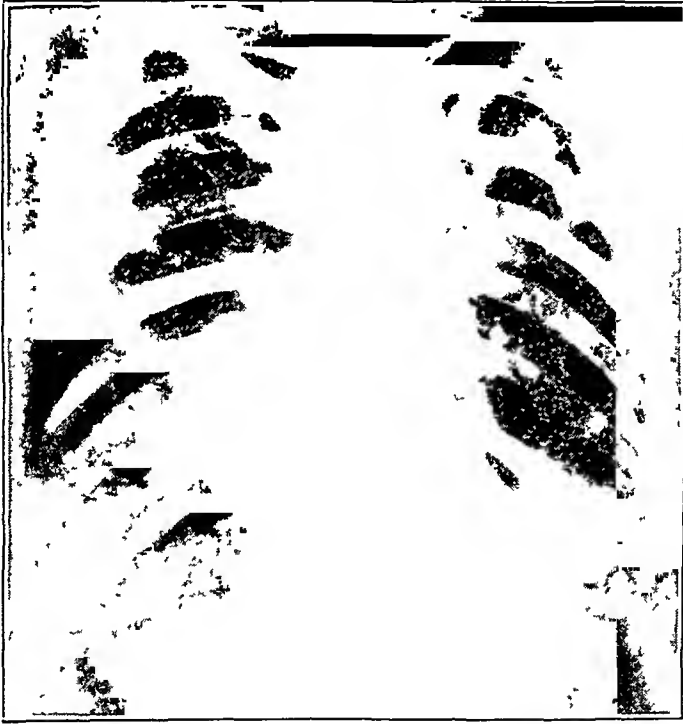


Fig. 6.—Roentgenogram made nineteen months after onset. Large masses are apparent in both lungs. Tissue from the area in the left lung was aspirated for biopsy.

*Necropsy.*—The lymph nodes of the neck, axillas and groin were not enlarged. There was a superficial cutaneous ulcer 6 by 4 cm. on the abdomen and three cutaneous nodules on the right knee. Both the ulcer and the nodules were similar to the ones already described.

The serous cavities were normal except for a few adhesions in the right pleural cavity. The mediastinal lymph nodes were slightly enlarged, but the cut surfaces showed nothing unusual. The lymph nodes in the mesentery, in the hilus of the liver and along the entire aorta measured up to 2 cm. in diameter. They were firm and matted together, and the cut surfaces were homogeneously pinkish gray except in some nodes where there were necrosis and hemorrhage.

The lungs, kidneys and liver contained scattered tumors. Those in the lungs were situated immediately beneath the pleura and in the outer portions of the parenchyma. They were predominant in the lower lobes. In the kidneys they were situated in the cortices; in the liver they were diffuse. They were firm, gray and sharply circumscribed and measured up to 2 cm. in diameter. Some showed beginning necrosis and hemorrhagic extravasation. In addition, the liver

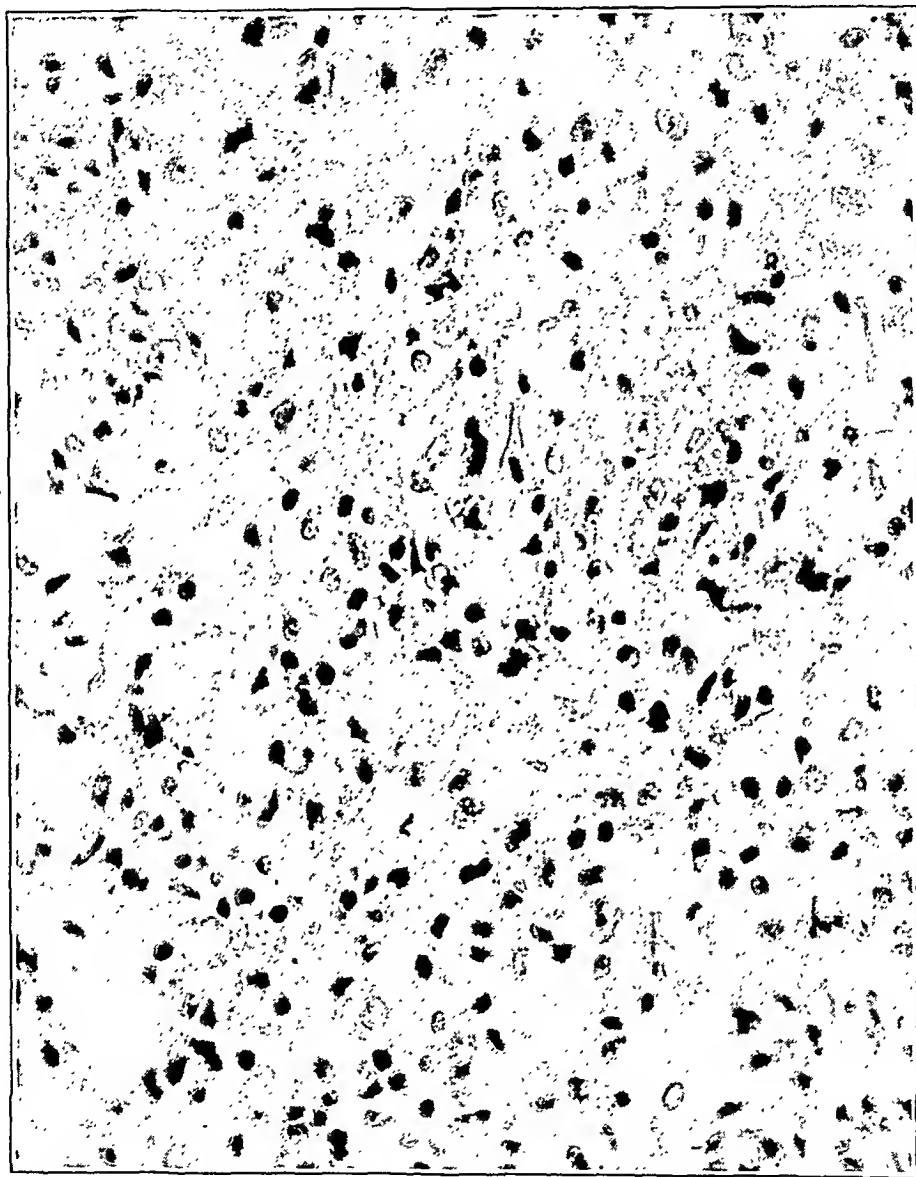


Fig. 7.—Tissue obtained by aspiration of the pulmonary mass shown in fig. 6 ( $\times 500$ ). The lesion is composed mostly of fibrous tissue, with some edema, slight necrosis and inflammatory cells, chiefly lymphocytes, plasma cells and a few monocytes. An occasional eosinophil and rare giant cells are present. Some of the monocytes contain abundant cytoplasm which is lacelike and vacuolated and seems to contain lipid material. The lesion resembles those in the skin (fig. 4).

contained several large masses 4 and 5 cm. in diameter the central portion of which were completely necrotic. The spleen was firm, weighed approximately 700 Gm. and on section was homogeneously dark red.

Histologically, the lymph nodes showed lesions typical of Hodgkin's lympho-granulomatosis. Their normal architecture was completely replaced with pleomorphic cells. These consisted of plasma cells, lymphocytes and other mononuclear cells, a few polymorphonuclear leukocytes and many mononuclear and multinuclear giant cells of the Reed-Sternberg type. There were no eosinophils. There was present, in addition, a varied amount of necrosis and hemorrhage, but fibrosis was not marked.

Necrosis with abscess formation was extensive in the lungs and in the liver and less so in the kidneys. A granulomatous process similar to that seen in the lymph nodes surrounded the necrotic areas. Giant cells, however, were sparse and were chiefly of the mononuclear variety. In the spleen the lymph follicles had almost disappeared. There were some generalized reticular fibrosis and a diffuse infiltration with pleomorphic cells. Reed-Sternberg giant cells, especially the multinucleated type, were numerous. There was no necrosis.

Sections of the cutaneous nodules were essentially the same as those made at biopsy and described previously. Outstanding features were the absence of eosinophils and the paucity of Reed-Sternberg giant cells. The few that were present were almost entirely mononuclear, like those seen in many granulomatous diseases.

#### COMMENT

As mentioned in the clinical discussion, differential diagnosis was confused. Panniculitis, sarcoid disease, reticuloendothelial cytomycosis (histoplasmosis), toxoplasmosis and mycosis fungoides were considered. Although Hodgkin's disease was early suspected, the histologic changes in the minute portions of tissue from the skin and lungs obtained for biopsy were not in themselves classic or pathognostic enough to confirm the impression. According to Kierland and Montgomery,<sup>2</sup> Reed-Sternberg cells may not be as typical in the skin as they are in the lymph nodes. Therefore, the diagnosis was established only at necropsy when the lesions in the skin and the lungs could be brought into relation with the typical ones in the abdominal lymph nodes.

Furthermore, lesions specific of Hodgkin's disease in the skin are as rare as nonspecific ones are common, and cases in which the first manifestation of the disease appears in the skin are rarer still. The literature on the subject is summarized by Fox,<sup>3</sup> Shelmire,<sup>4</sup> Miller,<sup>5</sup> Senear and Caro,<sup>6</sup> Kierland and Montgomery<sup>2</sup> and others. According to Miller and to Senear and Caro, several examples of "primary" spe-

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2. Kierland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease, *Proc. Staff Meet., Mayo Clin.* **16**:124-128 (Feb. 19) 1941.

3. Fox, H.: Lymphogranulomatosis of the Skin in Hodgkin's Disease, *Arch. Dermat. & Syph.* **2**:578-593 (Oct.) 1920.

4. Shelmire, B.: Hodgkin's Disease of the Skin, *South. M. J.* **18**:511-518 (July) 1925.

5. Miller, H. E.: Lymphogranulomatosis Cutis: Hodgkin's Disease, *Arch. Dermat. & Syph.* **17**:156-179 (Feb.) 1928.

6. Senear, F. E., and Caro, M. R.: Ulcerative Hodgkin's Disease of the Skin, *Arch. Dermat. & Syph.* **35**:114-128 (Jan.) 1937.

cific cutaneous Hodgkin's disease have been reported, but on close scrutiny there is considerable doubt as to diagnosis in some cases and in others the histologic nature of the lesions in the skin was not described. Even in the cases reported by Miller<sup>5</sup> and by Goeckerman and Montgomery<sup>7</sup> there was difficulty in differentiating the condition between mycosis fungoides, lymphosarcoma, leukemia and Hodgkin's disease. The case described here is, therefore, one of the few in which specific lesions in the skin preceded other manifestations of Hodgkin's disease. Two months elapsed before there was clinical evidence of visceral involvement, but whether in our case or in any case the disease can be regarded as strictly primary in skin is, of course, uncertain.

#### SUMMARY

A case of Hodgkin's disease of two years' duration is reported in which the first evidence of the disease appeared as specific lesions in the skin and fever. Eventually leukopenia, splenomegaly, hepatomegaly and pulmonary infiltration appeared. Abnormal swelling of the lymph nodes was never noted clinically, and at necropsy only the abdominal lymph nodes were involved. Relapsing, febrile, nodular panniculitis was suspected because of the unusual clinical course and dermatologic changes. Diagnosis was established at necropsy when the typical lesions of Hodgkin's disease in the abdominal lymph nodes were associated with the histologic changes in the skin and in the lungs noted at biopsy.

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7. Goeckerman, W. H., and Montgomery, H.: Cutaneous Lymphoblastoma: Report of Two Unusual Cases, *Arch. Dermat. & Syph.* **24**:383-395 (Sept.) 1931.



# Progress in Internal Medicine

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## VASCULAR DISEASES

EIGHTH ANNUAL REVIEW

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### REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

The present review of vascular diseases was compiled from the available literature accumulating between June 1, 1941 and June 1, 1942. A special effort was made to consider those articles which contributed new information, supplemented or confirmed present concepts or offered reasonable explanation of certain phenomena known to exist: This review should not be considered complete, as many deserving articles have undoubtedly been missed. Whenever possible, recognized omissions are usually corrected in a succeeding review. Articles on the dicoumarin 3,3'-methylenbis-4-hydroxycoumarin were not included in this review. They will be considered next year along with many unpublished papers on this drug now known to exist.

The Nomenclature Committee of the Section for the Study of the Peripheral Circulation of the American Heart Association<sup>1</sup> published a list of preferred and universal terms for designating diseases and abnormalities of the blood and lymph vessels of the extremities. Such a standardization of nomenclature is welcome but will undoubtedly be revised from time to time before a final listing will be acceptable to the majority of investigators in this field.

A 461 page monograph was recently published by di Cio,<sup>2</sup> of the University of Buenos Aires. It concerns mainly his experience with

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1. Nomenclature: Diseases and Abnormalities of Blood and Lymph Vessels of Extremities, *Am. Heart J.* **22**:549 (Oct.) 1941.

2. di Cio, A. V.: *Enfermedades de las arterias perifericas*, Buenos Aires, "El Ateneo," 1941.

400 cases of peripheral vascular disease, including the pathologic aspects, the clinical course and the results of treatment. It also contains a detailed description of the technic used and the results obtained with the author's new procedure for the injection of a carbon dioxide-oxygen mixture. The mixture is used in place of carbonic acid.

#### PHYSIOLOGY

*Reviews.*—An excellent review on the physiology of the peripheral circulation is presented by Hertzman.<sup>3</sup> A similar review by Hare and Hinsey<sup>4</sup> on the autonomic nervous system is recommended as being of value to those interested in this aspect of vascular diseases.

*Capillaries.*—McLennan and his co-workers<sup>5</sup> attempted to devise a new practical method for estimating blood pressure in the minute vessels of human beings during disease. This study was prompted by the many disadvantages of direct measurement of capillary blood pressure by means of a micropipette. A pressure plethysmograph is used, and the effect of graded external pressure on vascular volume is measured. Several pressure volume curves are thus obtained from which is computed not only the volume of blood but the pressure in the minute vessels of the forearm.

Fulton and Lutz,<sup>6</sup> using a microelectrode, stimulated the minute nerves leading to small blood vessels in the retrolingual membrane of the frog. Various united vascular responses were noted, generally dilation followed by constriction. As stimulation of the small nerves in the field of the microscope produced responses which are confined to restricted vascular patterns the authors consider the plexus to be physiologically discontinuous and the concept of smooth muscle motor units in small blood vessels likely.

Di Palma, Reynolds and Foster<sup>7</sup> studied the reactive capability of the smallest blood vessels of the skin by producing local ischemia of sufficient duration to elicit a given degree of reactive hyperemia. For this

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3. Hertzman, A. B.: The Peripheral Circulation, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 187.

4. Hare, K., and Hinsey, J. C.: The Autonomic Nervous System, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 407.

5. McLennan, C. E.; McLennan, M. T., and Landis, E. M.: The Effect of External Pressure on the Vascular Volume of the Forearm, J. Clin. Investigation **21**:319 (May) 1942.

6. Fulton, G. P., and Lutz, B. R.: Smooth Muscle Motor-Units in Small Blood Vessels, Am. J. Physiol. **135**:531 (Feb.) 1942.

7. Di Palma, J. R.; Reynolds, S. R. M., and Foster, F. I.: Quantitative Measurements of Reactive Hyperemia in Human Skin: II. Individual and Seasonal Variations, Am. Heart J. **23**:377 (March) 1942.

study, a series of three weights was applied to an area of skin and observations were made after release. Measurements were accurately calculated in seconds with a stop watch. The authors designated the stimulus time as the minimum period required to produce three areas of ischemia, uniform in color, size and sharpness. The clearing time was considered the time required for the resulting areas of reactive hyperemia to disappear. Average values for normal subjects were obtained.

The authors noted a seasonal variation in the clearing time, which lengthens in the fall, reaching a high level in December. During occlusion of the circulation for five to fifteen minutes with a tourniquet the stimulus time is unaffected, but the areas fail to clear. After release the stimulus time is lengthened. This is explained on the assumption that a dilating substance is released during occlusion but cannot be brought into contact with the blood vessels unless the flow of blood is reestablished. After releasing the tourniquet this substance in the smaller vessels is constantly being washed away, producing a deficit responsible for the local ischemia. Reflex or direct heat shortens the stimulus time, just as warmer weather does.

The capillaries of 8 women suffering from myxedema with typical myxedematous heart disease were studied by Zondek, Michael and Kaatz.<sup>8</sup> In 7 women the capillaries were markedly narrowed and greatly reduced in number, and in some instances only the loops were recognizable. On administration of thyroidin the capillary picture and circulation time gradually returned to normal. The authors are of the opinion that thyroidin is active in opening arteriovenous anastomoses coincidental with increased oxygen requirement.

LeCompte<sup>9</sup> studied the mechanism of the return of vascular tone in denervated ear vessels of rabbits and sympathectomized cats. His results supported the thesis of Grant, who stated the belief that the return of "tone" in sympathectomized blood vessels is due to a return of reactivity or a heightened responsiveness to humoral stimuli. LeCompte failed to find any evidence of a myogenic or intrinsic tone but is of the opinion that the return could best be explained as a response of the sensitized smooth muscle of the vessel wall to circulating vasoconstrictor substances. These substances were most likely epinephrine and sympathin.

In his experiments he utilized as an index of vasoconstriction not only the diameter of the ear vessel but surface temperature. Moderate changes in body temperature had no effect on the denervated vessels, but excitement or struggle produced vasoconstriction. This change

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8. Zondek, H.; Michael, M., and Kaatz, A.: The Capillaries in Myxedema, *Am. J. M. Sc.* **202**:435 (Sept.) 1941.

9. LeCompte, P. M.: Observations on the Return of Vascular Tone After Sympathectomy, *Am. J. Physiol.* **135**:43 (Dec.) 1941.

was also produced by epinephrine, but acetylcholine and pitressin were not effective. That circulating epinephrine was not entirely responsible was shown by the vasoconstriction produced by struggle in the sympathectomized cats, even though the adrenal glands were removed. In all of the experiments the sympathectomized animals were used promptly to avoid confusing results with those due to regeneration.

*Temperature Studies.*—Hyndman and Wolkin<sup>10</sup> studied the effects of heat, cold, epinephrine and pilocarpine on the cutaneous reactions of a series of patients who had had various operative procedures performed on the nervous system. Their studies concern three factors in heat regulation by the skin: sudomotor, vasomotor and pilomotor. An attempt was made to ascertain the governing systems, namely, (1) the end organ itself, (2) a reflex through the spinal cord and (3) central (hypothalamic) control. The results were obtained after the patients had been placed in a Burdick fever therapy cabinet, where obvious need for full dissipation of body heat occurred. The authors noted that the fingers and toes exhibit the greatest rise in temperature under these conditions. After unilateral sympathectomy the cutaneous temperatures of the fingers and toes are equal on the two sides after the heat treatment. This occurs regardless of their previous difference, provided these parts are contained in the heating cabinet. From this the authors concluded that the sympathectomized arteriole of the skin is capable of dilating as a result of the effect of heat on the vessel itself. As flushing and sweating occur on the normal side but not on the sympathectomized side, the authors concluded that active dilatation of central origin is the most likely mechanism. These capillary dilator fibers probably course through the anterior roots of the thoracolumbar nerves and thence through the sympathetic ganglions.

Similar studies were performed on these patients after placing them in a refrigerator.<sup>11</sup> The surface temperature was lowered bilaterally, but the sympathectomized side remained a few degrees warmer. That the temperature was lowered bilaterally indicates a local capillary response to cold, but that the normal side was colder indicates a central response. Of interest was the evidence that pain incident to cold is markedly reduced by sympathectomy, which suggested to the authors that the vasodilatation usually incident to sympathectomy does not account for the altered sensation.

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10. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: I. Effects of Heating the Body; Evidence for the Existence of Capillary Dilator Nerves in Anterior Roots, *Am. Heart J.* **22**:289 (Sept.) 1941.

11. Hyndman, O. R., and Wolkin, J.: The Autonomic Mechanism of Heat Conservation and Dissipation: II. Effects of Cooling of the Body; a Comparison of Peripheral and Central Vasomotor Responses to Cold, *Am. Heart J.* **23**:43 (Jan.) 1942.

In both of these reports Hyndman and Wolkin expressed the belief that body temperature under average or ordinary conditions, so far as the skin is concerned, is maintained largely by responses of the vessels themselves to external stimuli. The central mechanism functions (*a*) as a governor over the peripheral mechanism, and hence manifests itself more strongly when the need is extreme, and (*b*) as a device for utilizing or integrating the entire cutaneous surface for conservation or dissipation of heat when only a part is subjected to a changing temperature.

In a third communication Hyndman and Wolkin<sup>12</sup> reported studies on the behavior of the sympathectomized sides of subjects exposed to heat, cold and certain types of pain. They observed a definite alteration of sensation after sympathectomy. When the sympathectomized side was made objectively cold by refrigeration, it was not unusual for a patient to tell the authors that it felt warm. When heat was applied, the side which had been operated on felt slightly cooler than the normal side. The tolerance for cold was greatly enhanced on the sympathectomized side, as the aching and stinging pain normally present on exposure to severe grades of cold was greatly diminished.

*Blood Flow.*—A critical review of the theory and technic of the plethysmographic method of measuring blood flow was presented by Landowne and Katz.<sup>13</sup> They believe that valuable information can be obtained by this method of study if its limitations are appreciated and the results carefully interpreted. Its many errors are enumerated, but since they cannot be eliminated, certain necessary adjustments are suggested. A workable apparatus is described for studying the volume of blood flow in the human foot and leg, employing the method of Brodie and Russell as used by Hewlett and van Zwaluwenburg. Values for resting and for maximal volume flows in normal subjects are determined. The authors believe that under certain circumstances the caliber of central vessels may be the principal factor which determines the "maximal" volume of blood flow to a region. Their explanation is logical inasmuch as the flow to any region can be no greater than the cross section area of the vessel leading to that part. It can then be assumed that variations in maximal flow under different circumstances may therefore mirror changes in systemic pressure (driving force), express changes in peripheral resistance in the smaller vessels or indicate alterations in central arterial caliber. Under these circumstances patients with hypertension should have a greater flow than normal

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12. Hyndman, O. R., and Wolkin, J.: The Sympathetic Nervous System: Influence on Sensibility to Heat and Cold to Certain Types of Pain, *Arch. Neurol. & Psychiat.* **46**:1006 (Dec.) 1941.

13. Landowne, M., and Katz, L. N.: A Critique of the Plethysmographic Method of Measuring Blood Flow in the Extremities of Man, *Am. Heart J.* **23**: 644 (May) 1942.

persons, providing the caliber of a vessel remained unchanged and peripheral resistance did not increase. This is precisely what Abramson and Fierst<sup>14</sup> noted. They calculated the rate of resting blood flow in a series of 70 hypertensive and 90 normal subjects. The venous occlusion plethysmograph used was of the same type as that employed in previous studies. In hypertensive patients the flow in the forearm and the leg was greater than that in the control group. Similar responses were not obtained in the hand, as the flow was much less in hypertensive patients. The author concluded that patients with hypertension did not have the generalized and uniformly increased peripheral resistance which was previously thought to exist. They did not take into consideration the "driving force" of an increased blood pressure.

Abramson and Fierst<sup>15</sup> also studied the peripheral vascular responses to ingestion of a predominantly carbohydrate or protein meal. Blood flow was measured with the plethysmograph. The carbohydrate meal elicits no significant changes in the rate of peripheral blood flow in the hand, the forearm or the leg. On the other hand, there is a definite increase in the rate of oxygen consumption, in pulse rate and in pulse pressure. With the protein meal there is initially no change in the peripheral circulation, but later the rate of flow begins to increase, first in the hand and then in the forearm and the leg, usually remaining elevated until the end of the experiment. The changes in oxygen consumption, pulse rate and pulse pressure are similar to those observed with a carbohydrate meal, except that they are of greater magnitude.

Abramson<sup>16</sup> also studied the blood flow to different portions of the extremities following various peripheral vascular responses. The flow to the forearm and the leg is more constant than that to the hand. This is explained by the knowledge that the hand not only contains arteriovenous shunts but is more sensitive to changes in the vasomotor center. This makes the hand less satisfactory than the forearm and the leg for studying the local effect of sudden changes in the systemic circulation.

In association with Katzenstein and Ferris Abramson<sup>17</sup> made certain observations on reactive hyperemia in various portions of the extremities. These authors noted that the estimation of the blood flow repayment after a minute of arterial occlusion is of much greater value than obtain-

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14. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, *Am. Heart J.* **23**:84 (Jan.) 1942.

15. Abramson, D. I., and Fierst, S. M.: Peripheral Vascular Responses in Man During Digestion, *Am. J. Physiol.* **133**:686 (July) 1941.

16. Abramson, D. I.: Resting Blood Flow and Peripheral Vascular Responses in Different Portions of the Extremities, *J. Mt. Sinai Hosp.* **8**:328 (Jan.-Feb.) 1942.

17. Abramson, D. I.; Katzenstein, K. H., and Ferris, E. B., Jr.: Observations on Reactive Hyperemia in Various Portions of the Extremities, *Am. Heart J.* **22**: 329 (Sept.) 1941.

ing a figure which represents the single maximum response to arterial occlusion (percentage of blood flow debt repaid). In the forearm and the leg, and under certain conditions, in the hand, the magnitude of repayment was found to be directly proportional to the blood flow "debt" which was incurred. In contrast was the effect often noted in the hand, namely, that during the period of reactive hyperemia there was actually a reduction of blood flow to less than the control level. Direct application of heat would often produce a greater increase in blood flow to the hand than could be obtained by a period of arterial occlusion. The authors again considered this lack of uniform response of the forearm, the leg and the hand as indicative of the increased vessel tonus in the hand as compared with that of the forearm and the leg.

Abramson, Schkloven and Katzenstein<sup>18</sup> studied peripheral blood flow in a series of 29 schizophrenic patients, as well as in 23 other subjects with mental disease. In the majority of the psychotic patients the flow was markedly or moderately diminished in the hand but either normal or increased in the forearm and the leg. Exposing an extremity to local heat results in an increased flow in the hand which is equal to that obtained in normal subjects under the same conditions. The authors believe that their studies fail to demonstrate a lesion of the arterial tree at the periphery in the schizophrenic patients or in the other mentally ill patients studied. The reduced blood flow to the hand is again considered to be due to increased vascular tone, which could also explain the conflicting reports obtained in studies on the circulation time.

Stewart and Evans<sup>19</sup> studied peripheral blood flow in 6 patients in a myxedematous state. When the basal metabolic rate was low there was a definite decrease in blood flow, but as thyroid was administered the flow definitely increased. The results of this study are directly opposite to those previously described for hyperthyroidism.

Using the photoelectric plethysmograph, Hertzman<sup>20</sup> was able to demonstrate that the intermediate arteries of the hand, the dorsal metacarpal arteries and the digital arteries, do not participate in the vasoconstrictor reflexes of the hand. The latter reflexes were elicited chiefly by loud noises, immersion of the opposite hand in ice water or the application of cold to the finger studied. Hertzman explained this

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18. Abramson, D. I.; Schkloven, N., and Katzenstein, K. H.: Peripheral Blood Flow in Schizophrenia and Other Abnormal Mental States: Plethysmographic Study, *Arch. Neurol. & Psychiat.* **45**:973 (June) 1941.

19. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Myxedema as Compared with That in Hyperthyroidism, *Am. Heart J.* **23**:175 (Feb.) 1942.

20. Hertzman, A. B.: The Relative Responses of the Dorsal Metacarpal, Digital and Terminal Skin Arteries of the Hand in Vasoconstrictor Reflexes, *Am. J. Physiol.* **134**:59 (Aug.) 1941.

phenomenon by considering the vasomotor reflexes as highly selective with respect to the vascular topography involved in these reactions.

Burch and his associates<sup>21</sup> studied the spontaneous variations in volume of the tip of the right index finger, the tip of the right second toe and the posterosuperior portion of the right pinna on 12 normal white adults. Measurements were made with the plethysmograph, and all changes were considered to arise from intrinsic adjustments rather than as a result of stimuli deliberately applied. All of the parts studied undergo continuous variations in blood volume consisting of at least five separate rhythms. Two of these waves were simultaneous with the heart beat and with respiration, whereas the remaining three were simply designated as alpha, beta and gamma waves.

The mean frequency of the alpha waves is 7.9 per minute in the finger tip, 7.7 in the toe tip and 8.6 in the pinna. The mean volume of the deflections was 14.5 cubic millimeters per 5 cc. of finger, 7.1 cubic millimeters per 5 cc. of toe and 6.6 cubic millimeters per 5 cc. of pinna. The frequency of the beta deflections varied from 1 to 2 per minute and the size from 5 to 60 cubic millimeters per 5 cc. of tissue. The number of gamma deflections varied from 1 to 8 per hour and the volume from 50 to 350 cubic millimeters per 5 cc. of tissue.

The authors were unable to come to any definite conclusions as to the exact significance of these waves. Apparently they are related to functions of the autonomic and the central nervous system and also, probably passively, to the blood pressure. It was noted that in phlegmatic and stable persons the alpha waves were relatively small and varied little in size, whereas in excitable persons they were widespread in size and many were large.

In a second communication<sup>22</sup> a more detailed study of the alpha waves obtained from the records of 5 resting male subjects shows that in a five minute period concordant variations in size of this wave, as well as of the pulse wave, are startlingly low in the finger tips, while the percentage in the toe tips agrees in general with the previous estimates.

In a third article<sup>23</sup> the same authors studied the five types of rhythmic spontaneous variations in senile and in hypertensive patients.

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21. Burch, G. E.; Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip, and Postero-Superior Portion of the Pinna of Resting Normal White Adults, *Am. J. Physiol.* **136**:433 (May) 1942.

22. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of the Relationship Between the Pulse and Alpha Waves of the Tips of the Fingers and Toes of Five Adults, *Am. J. Physiol.* **136**:448 (May) 1942.

23. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of Quantitative Methods of the Spontaneous Variations in Volume of the Tips of the Fingers and Toes and Postero-Superior Portion of the Pinna of Hypertensive Patients, *Am. J. Physiol.* **136**:451 (May) 1942.



The waves were noted to be about the same as in normal subjects with the exception of the volume of the pulse waves to the toes, which was smaller. The latter observation was probably due to arteriosclerotic changes. The alpha waves were of interest. In the hypertensive subjects they resembled the waves observed in emotionally unstable and excitable normal adults, whereas the alpha waves of the senile subjects resembled those of stable subjects. Whether this is due to a sluggish psychosomatic state so well known in senile persons and also whether persons who are emotionally stable and not easily excitable live longer is a problem which was not studied.

Dauber, Weinberg and Landowne<sup>24</sup> studied the effect on pulse rate of applying and releasing occluding cuffs on the lower extremities in 27 normal subjects and 4 patients with thromboangiitis obliterans. Fifty-seven tests, each involving two or more occlusions, were performed with the subject in a horizontal position. Pulse rates were measured from electrocardiographic records. A rapid interruption of the arterial inflow was effected by connecting the wide cuffs, which were placed around the proximal thigh, to a tank of over 200 mm. Hg pressure. The immediate return of flow was assured by disconnecting the pressure tank and opening the cuff tube.

In about one half of the subjects application of the occluding pressure was followed by a slowing in pulse rate of 4 to 20 beats per minute (average 9), developing one to three seconds after occlusion and lasting five to sixteen seconds. During occlusion significant changes in pulse rate did not occur. On release of the occluding pressure a pulse acceleration of 15 to 30 beats per minute was noted in 97 per cent of the subjects, lasting one-sixth to three minutes. This acceleration commenced one to three seconds after release, reaching its maximum in four to five seconds. The extent and the duration of the pulse acceleration varied directly with the length of prior occlusion. No rise in pulse occurred on release of arterial occlusion in the 4 patients with thromboangiitis obliterans.

A fall in arterial blood pressure was observed to follow release of the arterial occlusion, and in 7 subjects studied by direct needle puncture of the brachial artery with a Hamilton manometer, the fall was observed to be instantaneous and the pulse contour changed as expected with a lowering of peripheral resistance. The blood pressure dropped from 12 to 35 mm. systolic and from 14 to 27 mm. diastolic. An instantaneous, transient rise in blood pressure occurred on induction of occlusion in the 5 subjects studied with the same technic.

It is concluded from the time at which the change in blood pressure and in pulse rate occurred that the pulse acceleration on release of

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24. Dauber, D. V.; Weinberg, H., and Landowne, M.: Effect on Pulse Rate of Peripheral Arterial Occlusion and Release, *Am. J. Physiol.* **133**:256 (June) 1941.

peripheral arterial occlusion is a reflex response to the drop in blood pressure and that the latter results from the lowering of the peripheral resistance by reopening the leg vascular channels. The failure of similar pulse acceleration to develop in patients with narrowing of the peripheral vessels would favor this interpretation.

Baldes and his co-workers<sup>25</sup> reported on their ten years' experience with blood flow in trained dogs under various conditions. Some of their work has been published previously but is worthy of repetition. Blood flow was measured with the thermostromuhr method of Rien but with a direct-current heater substituted for the conventional diathermy plates. Technically, they were able to measure blood flow with an error of no more than 10 per cent when the flow was not turbulent. In most of the experiments, the units were applied with the dogs under anesthesia and the studies performed for an indefinite time after recovery from the operation.

In general the flow of blood in a given vessel is directly proportional to the average blood pressure and inversely proportional to peripheral resistance. The velocity of blood flow is difficult to correlate with volume flow unless the size of the cross section of the blood vessel can be ascertained. The authors noted that if the area of cross section is reduced to 11 per cent, the blood flow will still remain more than one half of what it originally was. Rhythmic variations in blood flow were noted in many of the records, and it was concluded that they were due to rhythmic variations in the vascular bed, usually independent of blood pressure and respiration, and aggravated by a sudden noise or an intravenous injection of epinephrine. Exercise or the ingestion of a meal causes a marked increase in peripheral blood flow. Ether anesthesia increases the blood flow, and consequently results of studies made on subjects anesthetized with ether are often misleading. The flow is definitely increased after sympathectomy as well as during experimental thyrotoxicosis. Traumatic shock resulting from the manipulation of the intestines is followed by a definite decrease in flow. Pitressin given intravenously reduces blood flow markedly, but epinephrine produces variable results. It was the hope of the authors that these data will serve to emphasize the fact that blood flow to an extremity is influenced by many factors, any one of which, if altered, may profoundly affect the flow of blood to that region.

The effect of posture on blood flow in the lower extremities has been studied by a number of investigators, with little agreement as to results. Recently, Mayerson<sup>26</sup> reported the results of sixty experiments

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25. Baldes, E. J.; Herrick, J. F.; Essex, H. E., and Mann, F. C.: Studies on Peripheral Blood Flow, *Am. Heart J.* **21**:743 (June) 1941.

26. Mayerson, H. S.: The Influence of Posture on Blood Flow in the Dog, *Am. J. Physiol.* **136**:381 (May) 1942.

on 20 dogs, using the thermostromuhr to measure blood flow. These animals were anesthetized and tilted to the upright position with feet down. A consistent and marked decrease in the rate of blood flow was noted in the femoral vein and the femoral artery and a less pronounced fall in the carotid artery and the jugular vein. The author believes that the results provided direct evidence that as a result of compensatory orthostatic vasoconstriction there is a slowing of the volume flow to the subcardial regions, with a decrease in renal, gastric and intestinal activity. The decrease in flow on the arterial side is accompanied by a similar decrease in venous return due to pooling and stagnation in the capillaries and veins. The latter decrease is particularly marked if the upright position is maintained for more than relatively short intervals in the absence of adequate vasomotor and muscular tone.

*Diagnostic Tests.*—An excellent discussion of the value of the various diagnostic tests used in evaluating circulatory disorders was presented by Montgomery, Naide and Freeman.<sup>27</sup> Their study was based on the examination of 1,027 patients, of whom 75 per cent were found to have peripheral vascular disease. The technic and clinical significance of each test are discussed separately. Although history and physical examination are considered most essential, diagnostic tests give information on the degree of obstruction and formation of collateral circulation. In all cases of peripheral vascular disease either damage or repair may become dominant. Collateral circulation means functional repair. Vasodilating tests, the histamine test and reactive hyperemia tests are tests of function, and when past vascular damage is estimated by oscillometry, arteriography or palpation of pulses, these tests help to estimate the extent of collateral circulation. In many cases superimposed abnormal vasoconstriction unfortunately confuses the picture. The authors concluded that only by evaluating the circulation from the standpoint of past damage, its extent and location, repair, functional capacity and superimposed vasomotor tone, can the clinical status of each individual patient be entirely appreciated. Unfortunately, space does not permit a more detailed review of this entire article, but it is recommended to all persons interested in the significance and interpretation of the results obtained from these special tests.

The vasodilating tests for the relief of vessel spasm were also studied by Gootnick, Saland, Klein and Zurrow.<sup>28</sup> They compared the value of (1) the thermal reflex vasodilating test, (2) the sodium nitrite test

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27. Montgomery, H.; Naide, M., and Freeman, N. E.: The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease, *Am. Heart J.* **21**:780 (June) 1941.

28. Gootnick, A.; Saland, K.; Klein, C., and Zurrow, H.: Studies on Vasodilatation Tests in Peripheral Vascular Disease, *J. Lab. & Clin. Med.* **27**:878 (April) 1942.

and (3) the peripheral nerve block. Sodium nitrite injected intravenously and the hot water bath were found useful as preliminary tests for vasospasm. The thermal test is better suited for most patients, but the nitrite test is more dependable for patients who give the clinical impression of nonorganic vasospastic involvement. If either of these tests fails to give a normal response, then the nerve block is routinely used. The last-named test usually gives the most reliable information, and in many clinics throughout the country it is frequently used routinely.

Lange and Boyd<sup>29</sup> found fluorescein to be a satisfactory substance for determining circulation time and equally useful in establishing the presence and adequacy of local circulation. When injected intravenously it is nontoxic, and it is devoid of untoward effects when used in large doses. Its presence in the tissues can be easily determined by its fluorescence under ultraviolet light. In occlusive vascular diseases its presence or absence in the tissue is indicative of the blood supply to a given area. This is particularly valuable in ascertaining the level of occlusion. In regard to circulation time its value rests mainly on the fact that its use is an objective test devoid of the defects of other procedures. It is also of value in determining the circulation time in all types of experimental animal.

The authors report on the circulation times obtained on 256 subjects by injecting 2 to 4 cc. of the dye into an antecubital vein and watching for its appearance in the lips, tongue, gums or eyelids. These areas suddenly acquire a greenish yellow appearance under a mercury vapor lamp. The end point is sharply defined. The average circulation time in normal adults is seventeen and one-tenth seconds, in patients with cardiac failure thirty-nine seconds, in patients with hyperthyroidism ten and six-tenths seconds and in patients with hypothyroidism twenty-six seconds. These averages compare favorably with those obtained by established methods. The reviewer has had no experience with this substance, but these results of its use are worthy of consideration.

The application of direct heat to any ischemic limb is not without danger, as it frequently increases pain and accelerates gangrene. De Takáts and Miller<sup>30</sup> recently demonstrated with the plethysmograph that as much increase of blood flow can be obtained by applying indirect heat as by applying a heat cradle directly. This alleviates all of the dangers associated with direct heat and still produces the desired effect. The authors performed all of their studies on patients with different grades of arteriosclerosis, which is wise, inasmuch as this group is most frequently subjected to this form of therapy. A heat cradle of

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29. Lange, K., and Boyd, L. J.: The Use of Fluorescein to Determine the Adequacy of the Circulation, *M. Clin. North America* 26:943 (May) 1942.

30. de Takáts, G., and Miller, D. S.: Use of Direct Heat and Indirect Heat to Increase Blood Flow to the Extremities, *War Med.* 2:429 (May) 1942.

ample size was applied to the root of the affected limb and the abdomen proximal to the level of impaired circulation. Used in this manner it was found to be safe and effective.

Bennett, Hines and Krusen<sup>31</sup> applied short wave diathermy to the trunk of the human body and found it safe and efficient as a means of producing peripheral vasodilatation of the lower extremities. They advocate its use in the management and study of peripheral vascular disease. Although no data were given as to therapeutic results, the authors noted that the increased oral and cutaneous temperatures were not maintained for longer than thirty minutes after the cessation of diathermy. By proper insulation they believed the elevated temperatures could be maintained for several hours or longer. The use of this apparatus to induce reflex vasodilatation was compared with other methods now commonly used. Ten such studies were carried out; in eight of these diathermy succeeded in producing the desired effect, and in two it was obtained more quickly than with other methods of warming.

Various methods of applying diathermy were tried. The authors found the use of an electromagnetic cable in a pancake formation under the lumbosacral region to be the simplest and the most comfortable method of application. It is needless to say that this form of treatment must be given only under careful medical supervision.

Brown and Allen<sup>32</sup> introduced a new heating unit to produce reflex vasodilatation. It is tentatively called a "heating sleeve" or "heating boot" because of its appearance. It consists mainly of fine copper wire woven into a fireproof cloth, which is incorporated into a waterproof and washable cover. A transformer reduces the voltage to 10; a fuse protects against short circuits, and a thermostat included in the unit prevents the temperature from increasing to more than 43 C. The usual methods for testing its value in producing reflex vasodilatation were employed. When applied to one extremity the temperature of the skin of the digits of all the other extremities increases in most instances. The volume flow of blood of the opposite extremities also increases. Clinically, the apparatus is of value whenever controlled heat is indicated.

*Effect of Drugs.*—Abell and Page<sup>33</sup> used the moat chamber in normal rabbit ears to study the reaction of blood vessels to pressor agents.

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31. Bennett, R. L.; Hines, E. A., and Krusen, F. H.: Effect of Short-Wave Diathermy on the Cutaneous Temperatures of the Feet, *Am. Heart J.* **21**:490 (April) 1941.

32. Brown, G. E., and Allen, E. V.: Continuous Vasodilatation in the Extremities Produced Reflexly: Physiological Studies on Temperature of Skin and on Volume Flow of Blood, *Am. Heart J.* **21**:564 (May) 1941.

33. Abell, R. G., and Page, I. H.: The Reaction of Peripheral Blood Vessels to Angiotonin, Renin, and Other Pressor Agents, *J. Exper. Med.* **75**:305 (March) 1942.

Both renin and angiotonin in small doses cause constriction of the arterioles. Capillaries appear unaffected, while venules exhibit slight constriction or none at all with small doses and moderate constriction with large doses. The flow of blood through the tissues is not reduced except when large doses are administered. Parahydroxyphenylethylamine and methylguanidine sulfate in isopressor amounts act somewhat similarly. Isopressor amounts of epinephrine and pitressin, by contrast, elicit severe vasoconstriction of arterioles lasting longer than that due to angiotonin, but the flow of blood is sharply reduced or abolished altogether. The degree of venular constriction is also greater, while the capillaries remain unaffected. The vasoconstrictor action of angiotonin on the peripheral vessels, studied by this method, is indistinguishable from that of renin, except that it is more rapid. Abell and Page thus concluded that angiotonin is a substance capable of producing hypertension in that it is able to elevate arterial pressure by constricting the arterioles sufficiently to increase peripheral resistance but not sufficiently to reduce blood flow.

Krueger and his associates<sup>34</sup> repeated some of the older experiments on the effect of endocrine substances on gangrene produced by ergotamine tartrate in the tails of adult male and female albino rats. They found that the administration of testosterone propionate or estradiol benzoate does not influence the incidence, extent or rapidity of development of the gangrene in these animals.

According to Schwartz and his co-workers,<sup>35</sup> deproteinized pancreatic extract is relatively nontoxic when injected intravenously into rabbits. In most of the experiments massive doses were employed. The authors believe that the extract could probably be injected safely into human beings but suggest additional experimental work before its use is attempted.

Seldon, Lundy and Essex<sup>36</sup> studied the behavior of the minute blood vessels in the ears of rabbits under the influence of various anesthetic agents. Measurements were made through the Clark window. Simultaneous readings of the systolic blood pressure were also taken. Pentothal sodium lowered the blood pressure and dilated the arterioles and capillaries. Nitrous oxide had just the opposite effect. Cyclopropane

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34. Krueger, E.; Ludden, J. B.; Wright, I. S., and Wiland, J.: The Effect of Sex Hormones on the Production of Ergotamine Gangrene in Rats, *Am. Heart J.* **23**:164 (Feb.) 1942.

35. Schwartz, M. S.; Fisher, M. M.; Wright, I. S., and Duryee, A. W.: Deproteinized Pancreatic Extract (Depropanex): II. Effect of Intravenous Administration in Rabbits, *Am. Heart J.* **22**:122 (July) 1941.

36. Seldon, T. H.; Lundy, J. S., and Essex, H. E.: Effect of Certain General Anesthetic Agents on Small Blood Vessels in Ear of Rabbit, *Anesthesiology* **3**:146 (March) 1942.

and oxygen caused an increase in blood pressure and a decrease in the diameter of the arterioles, but the diameter of the capillaries was increased. When a mixture of ethylene and oxygen was used, a slight increase in the systolic blood pressure and a decrease in the diameter both of the arterioles and of the capillaries occurred. Blood circulated through the arterioles with apparently greater velocity during anesthesia with such a mixture than it did during a control period. Ether administered by the drop method increased the blood pressure and decreased the diameter of the arterioles, with an apparent increase in the velocity of the blood stream. The size of the capillaries was also decreased with a decrease in the velocity of the blood stream. The effect of ether is therefore somewhat similar to that of ethylene. The authors believe that the results of these experiments are in keeping with the oozing of blood during anesthesia, with special reference to pentothal sodium anesthesia.

Holman and Hewitt<sup>37</sup> substituted mercuric chloride for uranium nitrate and found that the former substance was also capable of producing necrotizing arterial lesions in dogs. In 1 of the 2 dogs studied an aneurysm developed at the site of one of these lesions.

Hoagland<sup>38</sup> demonstrated with the plethysmograph that the blood vessels of the hindlimb in cats are sensitized to intravenously injected acetylcholine after sympathectomy. After the administration of this drug a marked increase in the blood flow occurred far in excess of the control readings. This was not noted in acute experiments but could be elicited after the fifteenth day following operation. The author emphasizes the necessity of utmost care in doing sympathectomies in cats.

#### VASOSPASTIC DISORDERS

Leary and Allen<sup>39</sup> reported 4 cases of intermittent claudication apparently resulting from spasm induced by walking. In all of these cases the pulsations in the arteries diminished or disappeared on walking. In 2 cases the patients had aneurysms of the abdominal aorta, whereas in the other 2 the patients had chronic venous insufficiency as a result of previous thrombophlebitis. In no instance could any correlation between the associated pathologic condition and vessel spasm be demonstrated. The authors concluded that spasm must be considered the logical cause of claudication in all patients showing no

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37. Holman, R. L., and Hewitt, W. C.: Experimental Necrotizing Arteritis: II. Mercuric Chloride as Effective as Uranium Nitrate in Its Production, *Proc. Soc. Exper. Biol. & Med.* **49**:58 (Jan.) 1942.

38. Hoagland, H.: Sensitization of Blood Vessels to Acetylcholine by Sympathetic Denervation, *Proc. Soc. Exper. Biol. & Med.* **48**:326 (Oct.) 1941.

39. Leary, W. V., and Allen, E. V.: Intermittent Claudication as a Result of Arterial Spasm Induced by Walking, *Am. Heart J.* **22**:719 (Dec.) 1941.

evidence of occlusive vascular disease and having paradoxical reactions in the arteries elicited by exercise. If these conditions are not noted one must consider a localized obliteration of the smaller arteries in the involved musculature as the likely cause.

In keeping with this vein of thought is the work of Freeman and Montgomery<sup>40</sup> on the treatment of intermittent claudication by lumbar sympathectomy. In this study, which is also mentioned in the surgical review, the authors measured the severity of intermittent claudication in 12 patients with obliterative vascular disease of the lower extremities, both before and after blocking the lumbar sympathetic ganglions with procaine hydrochloride. All but 1 of the patients selected for this study presented evidence of abnormal vasoconstriction. The results of this study showed that 7 of the patients demonstrated improvement in their ability to walk, in 3 of them there was subjective improvement and in the remaining 2 no improvement was noted. These results were not adequately explained, and many theories were postulated.

The circulatory status of 8 patients with peripheral neuritis due to dietary deficiency was studied by Wilkins and Kolb.<sup>41</sup> Two additional patients with neuritis due to other causes were also included. Once full reflex vasodilatation was acquired, changes in cutaneous temperatures and blood flow were noted after the application of the various stimuli known to induce vasoconstriction in the digits. The results showed a decrease in the vasomotor tonus of the feet, resembling that occurring after incomplete sympathectomy. A delayed response to vasoconstrictor stimuli was also encountered in the toes of some of the patients. There was no rigid relation between the degree of vasomotor disturbances and the loss of sensation of muscular power. Definite improvement in the vasomotor disturbance usually occurs within two weeks of treatment. A complete return to normal vasomotor function usually requires a longer time.

Mulvey and Riely<sup>42</sup> describe the occurrence in a family group of an interesting syndrome known as status dysraphicus. It is a familial disorder in which the afflicted persons present a variety of degenerative constitutional signs consisting of vasospastic disorders in the extremities, disturbance of sensation in the lower limbs and feet and in a few members similar disturbances in the hands. Anomalies and slow-healing ulcers of the feet were also occasionally noted. It is difficult to distinguish from familial syringomyelia.

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40. Freeman, N. E., and Montgomery, H.: Lumbar Sympathectomy in the Treatment of Intermittent Claudication, *Am. Heart J.* **23**:224 (Feb.) 1942.

41. Wilkins, R. W., and Kolb, L. C.: Vasomotor Disturbances in Peripheral Neuritis, *Am. J. M. Sc.* **202**:216 (Aug.) 1941.

42. Mulvey, B. E., and Riely, L. A.: Familial Syringomyelia and Status Dysraphicus, *Ann. Int. Med.* **16**:966 (May) 1942.



## EFFECT OF COLD

In a series of three communications Lewis<sup>43</sup> describes his observations on the effects of cold on the skin and underlying tissues. Cold usually affects normal skin in two distinct ways. It may damage it by direct action, or it may cause it to freeze. The author stresses the distinction between these two effects, as they are commonly described together under the term frostbite. Normal skin can be injured by a reduction of its temperature without the intervention of mechanical injury to the cells. On exposure a local vasodilator substance is released. The resultant reaction is similar to the simplest forms of inflammation, characterized by heat, redness and swelling. The swelling may amount to as much as 15 per cent increase in volume, gradually subsiding in a few hours. Local pain and tenderness are not uncommon. The vasodilating substance is apparently related to the H substance. These are usually acute reactions and relatively transient. Cold allergy is probably related to this group.

The second type of reaction is neither transient nor simple. It includes "chilblains," "erythrocyanosis" (pernio) and "trench foot." All three of these conditions are separately considered but can be regarded as different manifestations of the same process, as all result from the prolonged action of cold. They have a great deal in common. In the early stages there is itching or tenderness, leading to coldness and vascular discoloration and proceeding to swelling, blistering and ulceration. Indolence of the lesions and slowness of healing are common. Their chief distinction lies in their location. Chilblains are found on the hands or other parts undergoing profound exposure. If the legs are involved, the lesions usually appear on the dorsum, especially in women who wear low shoes. Erythrocyanosis (pernio) is common in women and usually develops on the legs; it has been more prevalent since short skirts have been in vogue. In trench foot only the foot is involved after exposure to wet and cold. In the last-named condition freezing weather is not as important an etiologic agent as ordinary coldness with dampness or tight-fitting wearing apparel about the limbs. In all cases multiple exposures are almost as important a causative factor as prolonged exposure. Once any of these conditions has developed, recurrence is usual after exposure to cold of similar or even less severity.

Lewis also discusses the actual freezing of skin under the title of frostbite. This is readily produced by bringing the skin into contact with cold metal or by allowing a jet of cold air to impinge on it. The

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43. Lewis, T.: Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues: I. Reactions to Cold and Injury of Normal Skin, *Brit. M. J.* 2:795 (Dec. 6) 1941; II. Chilblains and Allied Conditions, *ibid.* 2:837 (Dec. 13) 1941; III. Frost-Bite, *ibid.* 2:869 (Dec. 20) 1941.

freezing point of skin is determined as being between 0 C. and — 2 C. Since the skin has the property of supercooling, the actual temperature necessary for freezing is much less. Frostbite occurs only when the air is dry and when the ground is snow clad or frozen. Wind favors its occurrence. The nose and ears are usually involved, whereas the feet are relatively free, since they are more commonly protected. The longer the exposure the more damage results. The end result of severe freezing, where there is deep penetration of the tissues, is necrosis. In the treatment of frostbite the well known gradual thawing is recommended. The object of this method is to restore the blood flow and warmth gradually and thus avoid vascular and accompanying reactions.

Greene<sup>44</sup> recently noted that the present war has produced two new disorders: immersion foot and shelter foot. The latter was described in last year's review under the term shelter legs. The former is related to frostbite and to trench foot. Its causes are the same, namely, cold, heat after cold, dampness, venous stagnation, wind, anoxia, nutritional deficiency and trauma. As in trench foot, dampness associated with cold and venous stagnation are probably the most important factors in the production of immersion foot. The treatment is similar to that for frostbite and needs no repetition. We find little difference between frostbite, immersion foot and trench foot except in the predisposing causes.

Careful pathologic studies have recently been reported to show that pernio and livedo reticularis are vascular diseases. Although the clinical pictures of these two diseases are different, there is a similarity of the pathologic changes in the arterioles of the skin. Each will be considered separately.

*Pernio*.—McGovern and Wright<sup>45</sup> describe the clinical picture and results of biopsy in 4 cases of pernio. In all of these cases lowered environmental temperatures resulted in extensive vascular changes in the smaller vessels of the skin, causing anoxemia of the supplied tissue, necrosis and ulceration. In some cases definite scleroderma-like changes ultimately develop. Characteristically, exacerbations of this condition occur in the fall and winter and regression takes place in the summer. In cases of long-standing disease complete recovery may not occur in the summer. Although this condition was considered a tuberculous lesion in the past, no evidence of this disease is found either clinically or roentgenologically. Giant cells were demonstrated in the pathologic sections but were considered to represent a chronic irritative process.

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44. Greene, R.: Frost-Bite and Kindred Ills, *Lancet* 2:689 (Dec. 6) 1941.

45. McGovern, T., and Wright, I. S.: Pernio: A Vascular Disease, *Am. Heart J.* 22:583 (Nov.) 1941.

The authors suggested the following tentative criteria for diagnosis of pernio:

1. It may occur in both sexes, predominantly in females.
2. It usually commences in adolescence or early adulthood.
3. It is associated with cool or cold weather and may show spontaneous recovery in warm weather.
4. The lesions have a predilection for exposed areas, particularly the lower third of the leg, around the internal malleolus and calf. They may extend down to the dorsum of the foot and toes, and up the legs to below the knees.
5. The clinical course of these lesions may be characterized briefly as (a) the formation of a reddened area which later becomes elevated, hard, and very painful; (b) this becomes violaceous and fluctuating; (c) it opens, producing an ulcer; (d) this oozes, drains, and heals, becoming less painful; (e) a violaceous scar remains; and (f) the following winter ulceration tends to recur in the same area.
6. There is a definite pathologic picture. Most characteristic is, first, an angiitis of the smaller vessels; secondly, necrosis of the fat; and, thirdly, the presence of giant cells.

No specific treatment of pernio is known. The authors obtained the best results by triweekly treatments with acetyl-beta-methylcholine chloride by iontophoresis and by protecting the legs from undue exposure with proper clothing. Living in a warm climate should be beneficial.

Barker, Hines and Craig<sup>46</sup> reported on a series of 13 cases of livedo reticularis. This circulatory disorder is characterized by a mottled, blotchy or reticular bluish discoloration of the skin which varies from deep blue when the patient is exposed to a cold environment to red or reddish-purple when he is in a warm environment. There is usually subjective, as well as objective, coldness of the skin. In mild forms the condition is present only during exposure to cold, whereas, in the more severe forms the color persists and is relatively unchanged by environmental temperature. The clinical manifestations differ distinctly from those of Raynaud's disease, acrocyanosis and thromboangiitis obliterans. These patients have no evidence of tuberculosis or syphilis, and the circulatory disturbance develops during adult life. The causation is not known.

Pathologic studies revealed organic changes in the arterioles of the skin, which, with chronic vasospasm, result in regional atony and dilatation of capillaries and slowing of the blood flow. The condition may be complicated by ulceration of the legs and superficial gangrene of the toes. In 2 cases the patients responded well to lumbar sympathetic ganglionectomy.

*Raynaud's Disease.*—The capillary response in 29 cases of Raynaud's disease was studied by Deutsch,<sup>47</sup> before and after sympathe-

46. Barker, N. W.; Hines, E. A., Jr., and Craig, W. M.: Livedo Reticularis: A Peripheral Arteriolar Disease, *Am. Heart J.* **21**:592 (May) 1941.

47. Deutsch, F.: Capillary Studies in Raynaud's Disease, *J. Lab. & Clin. Med.* **26**:1729 (Aug.) 1941.

ectomy. All of the measurements were made under a capillaroscope which was equipped for calibration and photography. In addition to the routine observations, the flow in the capillaries was studied after occluding the arterial and the venous flow by the use of a blood pressure cuff quickly pumped up to 30 mm. above systolic blood pressure. The term reflux time was introduced as the time which elapses before capillary flow ceases, whereas the term critical capillary pressure was used to denote that pressure at which the flow once again reappears when the cuff in the foregoing experiment is gradually decompressed at the rate of 10 mm. per two seconds.

On the basis of his studies the author believes that the capillary changes in Raynaud's disease are an earlier manifestation of the disease than the clinical symptoms. He was also able to define the severity of the disease more accurately by this method than by studying the gross clinical findings. In the majority of cases of Raynaud's disease he noted a persistence of the subpapillary plexus and a persistent connection between it and the outgrowing capillaries.

Preganglionic sympathectomy has a distinct influence on the capillary picture of Raynaud's disease. In 12 cases the speed of the blood flow increased. In 10 of 15 cases the width of the capillaries decreased. The author suggests that these changes explain the previously mentioned postoperative pallor and higher temperature of the hand following the surgical procedure. Other changes following operative intervention are as follows: In cases with a slow reflux time, the time increased, and vice versa; the capillary permeability decreased, and the excretory ducts of the sweat glands failed to dilate. As a rule all of these changes became less distinct as time went on. The subjective symptoms of the patient are to some extent independent of this clinical picture, as in some cases the patients were relieved of their complaints but no changes were noted in the capillaries.

Hyndman and Wolkin<sup>48</sup> had the opportunity of studying 3 patients with Raynaud's disease while doing their research on the mechanism of heat conservation and dissipation already reviewed in the section on physiology. Temperature studies were made on these patients after submitting them to the heating and to refrigeration. All had previously had sympathectomies on one side only. The results are not unlike those previously reviewed. The authors are of the opinion that the evidence obtained is greatly in favor of the conclusion that the disease is primarily a vascular and not a sympathetic disorder. Sympathectomy is beneficial objectively because it eliminates the vasomotor influence, which is normal in any given case. It is beneficial subjectively because it abolishes the aching and stinging pain of vasoconstriction. After sympa-

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48. Hyndman, O. R., and Wolkin, J.: Raynaud's Disease, *Am. Heart J.* **23**:535 (April) 1942.

thectomy the hands still retain the local disorder objectively, as cold continues to cause color changes. This was further substantiated by the observation that when a nude subject is placed in a refrigerator and kept long enough to cause a fall in central temperature and at the same time one of his hands is kept at room temperature, the hand does not show evidence of vascular spasm, either subjectively or objectively, even though the exposed hand reacts severely.

Altschule and his associates<sup>49</sup> noted that the lung volume and pulmonary dynamics did not change in 3 patients with Raynaud's disease on exposure to cold. Of the 3 patients studied, 1 had evidence of diffuse pulmonary fibrosis with a striking decrease in pulmonary dynamics under ordinary conditions whereas the other 2 had no evidence of a pathologic condition in the lungs. The authors believe that their findings indicated that the blood vessels of the lungs do not react in a manner similar to those of the hands and feet. These findings were further substantiated by the observation that the circulation time through the lungs did not change on exposure to cold.

#### ARTERIOSCLEROSIS

An excellent review on the concept of the chemical changes occurring in atheromatosis was recently presented by Page.<sup>50</sup> In this article the author attempts to answer most of the most pertinent questions on the subject. Leary<sup>51</sup> also presented an extensive review on the genesis of atherosclerosis. To review either of these with their many considerations and pathologic studies is not feasible. Leary's summary is worthy of repetition for in it he presents the following evidence:

That atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells, which first appear in the intima of the arterial wall.

That cholesterol is esterified in the liver as directly observed in the experimental rabbit.

That cholesterol when fed in excess to rabbits is deposited in the form of esters in the cells of the liver and adrenals.

That the esters as they accumulate in excess become a burden and are removed from these organs by Kupffer cells in the liver and their analogues in the adrenals.

That the cholesterol esters are engulfed as particulate matter by these cells.

That these cells, now lipid cells, escape from the liver and adrenals through the blood and lymph systems and may produce obstruction in the lymph sinuses.

That lipid cells, having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses but

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49. Altschule, M. D.; Linenthal, H., and Zamcheck, N.: Lung Volume and Pulmonary Dynamics in Raynaud's Disease: Effect of Exposure to Cold, *Proc. Soc. Exper. Biol. & Med.* **48**:503 (Nov.) 1941.

50. Page, I. H.: Some Aspects of the Nature of the Chemical Changes Occurring in Atheromatosis, *Ann. Int. Med.* **14**:1741 (April) 1941.

51. Leary, T.: The Genesis of Atherosclerosis, *Arch. Path.* **32**:507 (Oct.) 1941.

is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters.

That the latent period after the beginning of cholesterol feeding in the rabbit and before aortic lesions appear is dependent on the production of esters in excess and their transport, as indicated in paragraphs 2 to 7 inclusive.

That lipid cells possess the power to split cholesterol esters and bring the substance into solution in an excess of fatty acids.

That excess cholesterol esters are akin to silica in their irritant character. Both are difficult of metabolism, tend to stay long in tissues and stimulate a growth of connective tissue.

That intravenous silica and cholesterol esters, practically alone among particulate matters, tend to cause in rabbits cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of chronic "interstitial" nephritis.

That human atherosclerosis is associated with intermittent accretions of excess cholesterol esters in contrast to the continuous accretions in the rabbit fed cholesterol. That the differences in the appearance of atherosclerotic lesions in the two species are due in great part to differences in the manner of feeding. Diffuse lipoidosis is more common in the experimental rabbit, partly for the same reason.

The accepted criteria for the establishment of a causal relation between a given agent and a disease are embodied in Koch's laws. Since animals are not susceptible to all human infections, or because evident parasites cannot be cultivated, or for other reasons, various compromises have been made with these postulates. However, the evidence of a causal relation is most complete when Koch's laws can be satisfied.

In the causation of atherosclerosis the principles of Koch's laws can be fulfilled. Excess cholesterol is always present in the active stages of human atherosclerosis. It can be identified in the lesions as definitely as can the bacterial or other parasitic agents producing infections. It can be extracted from the lesions. Human arterial lesions can be reproduced experimentally by its use with more exactness than the lesions of many human infections can be reproduced by the introduction into susceptible animals of their recognized causal agents. It can be identified in and extracted from the experimental lesions.

Stresses determine the localization of lesions and influence the degree of the sclerotic processes. The efficiency of cholesterol metabolism is modified by sex and thyroid factors. Age (time plus thyroid deterioration) and heredity are also contributing elements.

In another communication Leary<sup>52</sup> suggests that since arteriosclerosis is the "cholesterol disease" of human beings, a diet limited or lacking in cholesterol should prevent arteriosclerosis. Vegetable oils, the stérols which are not absorbed, can be substituted for animal fats.

Wilens<sup>53</sup> has a slightly different idea on the location of atheromatous lesions. He believes that the intimal lipids, whether extracellular or contained within mobile phagocytes, tend as a result of the pulse movements of the vessel to converge or migrate toward points of least mobility, being impeded in their progress at points where firm scars have fused the

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52. Leary, T.: Arteriosclerosis, *Bull. New York Acad. Med.* **17**:887 (Dec.) 1941.

53. Wilens, S. L.: Distribution of Intimal Atheromatous Lesions in Arteries of Rabbits on High Cholesterol Diets, *Am. J. Path.* **18**:63 (Jan.) 1942.

media to the intima, obliterating potential tissue spaces. Although this idea is not new, it is in opposition to the belief that atheromatous lesions usually develop in places of greater stress and strain. It was Wilens' opinion that since the greatest atheromatous lesions develop in places where the arteries are the least movable, laboratory studies on rabbits could be done to demonstrate this phenomenon. The rabbits were fed cholesterol to stimulate the formation of atheroma, and portions of the femoral and carotid arteries were rendered relatively immobile by being invested in cylindric silver cuffs. The results confirmed his opinion, as the lipids localized in the intima of the arteries in the region of the cuffs in all but 7 of the 36 arteries studied.

Hueper<sup>54</sup> also presented evidence to support the

. . . thesis that the fundamental and general causal mechanism of degenerative arterial disease is an impaired nutrition and oxygenation of the vascular wall, resulting in endothelial damage, increased intimal permeability, and the infiltration of plasma into the subintimal tissue followed by the proliferation of endothelial cells and the degeneration of the muscular and elastic elements of the media. If the plasma contains persistently or transiently pathologically large amounts of cholesterol or physicochemically related substances forming emulsions with the plasma, there occurs a retention of this material in the proliferating endothelial cells with the ultimate formation of atheromas, representing thus a special morphological variety of arteriosclerosis. The second morphological type of arteriosclerosis, on the other hand, is caused by highly excessive contraction or relaxation of the arterial wall through the action of hypertonic or hypotonic agents, respectively, giving rise to the development of primary medial necroses and calcifications. The secondary calcification of medial necroses is hastened and enhanced, if the primary causal vasculotonic factor (parathyroid hormone, vitamin D) produces at the same time a disturbance in the calcium metabolism or if a high blood calcium level is present normally as in herbivorous animals. Type and dose of the etiologic agents thus influence to a certain extent the morphological type of the resulting arteriosclerotic lesion.

The following etiologic agents are suggested by Hueper: 1. Chemically inert, film-forming and emulsion-forming agents (cholesterol, polyvinyl alcohol, methyl cellulose and, possibly, pathologic, large molecular protein complexes) present in the plasma impair the gaseous and nutritive exchange in the interface of blood and vascular wall. 2. Hypertonic agents cause not only an excessive densification of the vascular tissue with an exaggerated functional and metabolic stimulation of its component elements but a compression of the vasa vasorum resulting in ischemic hypoxemia and aggravating disturbances in the diffusibility of the vascular tissues by nutritive and waste metabolites. These include epinephrine, solution of posterior pituitary, renin, ephedrine, ergot, digitalis and compounds containing lead. 3. By an excessive dilatation of the vascular walls hypotonic agents produce a compression of the

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54. Hueper, W. C.: The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis, *Medicine* 20:397 (Dec.) 1941.

collapsed vasa vasorum, a slowing of the blood flow and a lowering of the blood pressure, causing thereby stagnant anoxemia in the vascular wall and impaired gaseous exchange between the blood and the surrounding vascular tissues. Histamine, acetylcholine, nitrites, methylxanthine, caffeine and barbiturates are used. There is also evidence that carbon monoxide and reduced atmospheric pressure may well be included in this group.

Hueper believes that in certain cases a rational therapeutic management of arteriosclerotic patients could be accomplished providing the etiologic agent could be determined. Occupational arteriosclerosis, such as is present in workers employed in tobacco and chemical industries, is amenable to treatment. Iodine preparations and thyroid have proved so far to be the most suitable agents in preventing the development or arresting the progress of arteriosclerosis of various causation. There is, however, no evidence to show that they will cure the disease. The effect of these agents lies purely in the maintenance of an adequate oxygen metabolism, and consequently the best results are obtained when the latter condition is at fault.

Bruger and Rosenkrantz<sup>55</sup> suggest the possible relation of the advent of arteriosclerosis to the decreased activity of the thyroid so commonly associated with advancing age. They reviewed the records of 24,000 determinations of basal metabolic rate and found that 775 were made on patients 55 years or older. Of this group 293 were accepted for analysis. The charts of these patients were studied, and 223 were found to have arteriosclerosis and 70 to be without. A pronounced decrease in the average basal metabolic rate was noted in the former group, especially in patients over 70. Although no definite conclusion is reached, the authors submit many theoretic considerations especially related to the receptibility of the vascular tree to the deposition of lipids the concentration of which depends on thyroid activity.

Masson<sup>56</sup> found that arteriosclerotic vessels have a great affinity for iodine, being somewhat similar in that respect to syphilitic and to tuberculous tissue. All of his experiments were performed on rabbits. Of 6 rabbits who were free from arteriosclerosis 5 were given potassium iodide and 1 was not. In 3 the aorta was free from iodide, and in the other 3 only small quantities could be detected. In another group of rabbits made arteriosclerotic with cholesterol and given iodides, it was always possible to demonstrate a greater iodide content in their aortas than in those of the nonarteriosclerotic group.

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55. Bruger, M., and Rosenkrantz, J. A.: Arteriosclerosis and Hypothyroidism: Observation on Their Possible Relationship, *J. Clin. Endocrinol.* **2**:176 (March) 1942.

56. Masson, P.: Iodine Distribution in Normal and Sclerotic Vascular Walls, *Schweiz. med. Wchnschr.* **71**:1042 (Sept. 6) 1941.



Ludden, Bruger and Wright<sup>57</sup> continued their studies on experimental atherosclerosis and found that when female rabbits are fed cholesterol, the development of hypercholesterolemia is inhibited and the deposition of cholesterol in the aorta is prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol these steroids exert little such protective action or none at all.

Daft and his associates<sup>58</sup> give a brief but interesting report on the occurrence of extensive hyaline sclerosis and calcification of blood vessels in 7 young rats observed in the course of some preliminary experiments with purified diets deficient in the vitamin B complex and containing 1 per cent sulfaguanidine (sulfanilylguanidine), supplemented with thiamine, riboflavine, pyridoxine, pantothenic acid, nicotinic acid and choline. This mixture was given continuously for sixty-two to one hundred and ninety-two days prior to autopsy. The sulfaguanidine is considered the etiologic agent.

The incidence and complications of occlusive peripheral arteriosclerosis among diabetic and nondiabetic patients was studied by Dry and Hines.<sup>59</sup> In all cases they assumed arteriosclerosis to be present, as their main concern was to compare the severity or degree of impairment in the two groups. They studied 230 diabetic and 219 nondiabetic patients with conditions given the diagnosis of occlusive peripheral arteriosclerosis. They found that the absolute incidence of arteriosclerosis to a degree of causing arterial insufficiency is significantly higher in the so-called "diabetic group" in every decade when diabetic patients are compared to nondiabetic patients as a group. The ratio for the entire group is approximately 11:1. Arteriosclerosis obliterans occurs a decade later among nondiabetic patients as a group than it does among diabetic patients. It occurs two decades later among nondiabetic women than it does among diabetic men, and it occurs one decade later among nondiabetic women than it does among diabetic women. The incidence of arteriosclerosis obliterans among diabetic women is almost eighty times as frequent as it is among nondiabetic women as a group. Even in the age period of as early as 40 to 49 years, arteriosclerosis obliterans is about twelve times as common among diabetic women as it is among nondiabetic men. The ratio of men to women in the nondiabetic group is approximately 7:1, whereas the

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57. Ludden, J. B.; Bruger, M., and Wright, I. S.: Experimental Arteriosclerosis: IV. Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis in Rabbits, *Arch. Path.* **33**:58 (Jan.) 1942.

58. Daft, F. S.; Ashburn, L. L.; Spicer, S. S., and Sebrell, W. H.: The Occurrence of Hyaline Sclerosis and Calcification of Blood Vessels in Rats on Sulfaguanidine, *Pub. Health Rep.* **57**:217 (Feb. 13) 1942.

59. Dry, T. J., and Hines, E. A., Jr.: Role of Diabetes in the Development of Degenerative Vascular Disease, *Ann. Int. Med.* **14**:1893 (April) 1941.

ratio is 2:1 for the diabetic group. The incidence of gangrene or trophic ulcers in the diabetic group is 62.1 per cent and in the non-diabetic group 48.9 per cent. Seventy-nine and four-tenths per cent of the diabetic women have this complication. Diabetic retinitis and diabetic peripheral neuritis also occur with great frequency among diabetic patients afflicted with arteriosclerosis obliterans.

The authors postulate that a biologic background exists for the development of advanced arteriosclerosis in the presence of diabetes mellitus. Apparently, it is an inherent weakness, or an abiotrophy exists which affects both the insulin-producing tissues and the vascular system and which requires in each instance only an additional stimulus to bring about pathologic changes. This stimulus may be obesity, an infectious illness, overfeeding, hypertension or hyperlipemia. Dry and Hines also consider a common mechanism for the production of the frequently associated arteriosclerosis obliterans, retinitis and peripheral neuritis in diabetes. This consists of the involvement of the nutrient vessels, namely, the retinal arterioles in retinitis, the vasa nervorum in neuritis and the vasa vasorum in intimal arteriosclerosis.

Kauvar<sup>60</sup> also believes that arteriosclerosis and the resultant ischemia represent a major cause in the production of diabetic neuritis. His data were obtained from a study of 150 patients, of whom 65 had diabetes, 80 had generalized arteriosclerosis and 5 had a deficient blood supply to the extremities not due to arteriosclerosis or diabetes. In this study evidence of peripheral neuritis was found in 18 per cent of the patients with diabetes, in 8 per cent of the patients with generalized arteriosclerosis without diabetes and in all the patients with grossly deficient blood supply to the extremities.

Meyers and Altshuler<sup>61</sup> tabulated the incidence of peripheral vascular disease in 74 diabetic patients. Thirty-two (43 per cent) were found to have varying degrees of vascular insufficiency. Of this group, 13 (41 per cent) had no symptoms but showed evidence by careful study. The incidence of this complication increased with the age of the patient, but no correlation was observed between the severity of the diabetes and the presence of peripheral vascular disease.

That serum potassium is the substance responsible for pain in ischemic tissue was considered likely by Harpuder and Stein.<sup>62</sup> They arrived at this conclusion by studying a sample of blood drawn from an antecubital vein after ischemic exercise of the arm. Samples were

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60. Kauvar, A. J.: The Relation of Arteriosclerosis to Diabetic Neuritis of the Lower Extremities, *J. Clin. Endocrinol.* **1**:955 (Dec.) 1941.

61. Meyers, M. P., and Altshuler, S. S.: Peripheral Vascular Studies of the Lower Extremities in Diabetic Patients, *Harper Hosp. Bull.* **1**:40 (Dec.) 1941.

62. Harpuder, K., and Stein, I. D.: Studies on the Cause of Pain in Ischemia, *Arch. Phys. Therapy* **23**:218 (April) 1942.

taken (1) during rest, (2) ten seconds after ischemic exercise and release of circulation and (3) three minutes later. Of many substances investigated, potassium was the only chemical to increase during exercise, being 20 to 25 per cent higher during this period. As details concerning the number of cases investigated and the exact chemical figures are not included, little can be said concerning the authenticity of this hypothesis.

#### EMBOLISM AND THROMBOSIS

Garvin<sup>63</sup> investigated the relative importance of mural thrombi as a source of emboli. He studied the problem indirectly on the assumption that if mural thrombi are an important source of emboli, then patients having mural thrombi should have a significantly higher incidence of infarction of the various viscera than a control group would have.

He then examined the clinical and pathologic records of 771 consecutive adult patients who died of heart disease and were examined post mortem. The incidence of pulmonary infarction was found to be three times as frequent in those patients with mural thrombi in the right side of the heart as in those patients without. Infarcts of the brain, kidneys, spleen, intestines and extremities were more than twice as common in patients with mural thrombi in the left side of the heart as in patients without such thrombi in this location. These observations were indicative to the author that mural thrombi in the heart are a significant cause of embolic occlusion of arteries both in the lesser and in the greater circulation.

There is increasing evidence that arterial obstruction rather than venous obstruction plays a significant role in the causation of Volkmann's contracture. Horwitz'<sup>64</sup> recent studies lend support to this concept in that he was able to demonstrate a widespread venous anastomosis in the elbow region in normal persons which was not only well protected between the muscle planes but external to the confines of the antecubital space.

In the present review we have not attempted to cover the literature on cervical ribs and thrombosis of subclavian vessels. A case reported by Hoobler<sup>65</sup> was of interest. A patient had cervical ribs and throm-

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63. Garvin, C. F.: Mural Thrombi in the Heart as a Source of Emboli, *Am. J. M. Sc.* **201**:412 (March) 1941.

64. Horwitz, T.: The Significance of the Venous Circulation About the Elbow in the Pathomechanics of Volkmann's Contracture, *Surg., Gynec. & Obst.* **74**:871 (April) 1942.

65. Hoobler, S. W.: The Syndrome of Cervical Rib with Subclavian Arterial Thrombosis and Hemiplegia Due to Cerebral Embolism, *New England J. Med.* **226**:942 (June 11) 1942.

bosis of the right subclavian artery which was complicated two years later by hemiplegia due to a cerebral embolism.

Aggeler, Lucia and Thompson<sup>66</sup> described a syndrome resulting from the occlusion of all of the vessels arising from the arch of the aorta. The condition was characterized by complete absence of pulsations in carotid arteries and in the arteries of both upper extremities. Symptoms referable to the central nervous system, ocular manifestations, atrophic rhinitis and atrophy of the arms and legs are usually present. In the case described by these authors the exact causation was not known, but the condition was thought to result from thrombocytosis and autohemagglutination.

Cases of gangrene of a digit secondary to local anesthesia were reported by McLaughlin<sup>67</sup> and Perner.<sup>68</sup> This unfortunate complication prompted the latter author to investigate the effect of injection of various anesthetic agents into the base of a rat's tail. Thirty male rats were given injections of 1 and 2 per cent procaine hydrochloride with epinephrine in the concentrations usually marketed or without epinephrine at all, as well as with physiologic solution of sodium chloride and with epinephrine in a concentration of 1:10,000. No cases of gangrene of the tail were encountered in the rats given injections either of 1 or of 2 per cent procaine hydrochloride or of saline solution. Of the remaining 21 rats, gangrene of the tip of the tail developed in 10 within thirty-six hours after receiving procaine hydrochloride with epinephrine. The author concluded that epinephrine should not be used in anesthetic mixtures in any concentration for operations on the fingers or toes.

Gangrene of the extremities in the newborn has been occasionally encountered. Recently Heller and Alvari<sup>69</sup> reported a case of such a condition in which the causation remained obscure. They believe that it was either due to pressure on the limbs from a long and difficult labor or secondary to infection.

#### AINHUM

A case of ainhum is reported by Davies and Hewer.<sup>70</sup> In this case the patient was a 55 year old Negro with evidence of generalized

66. Aggeler, P. M.; Lucia, S. P., and Thompson, J. H.: A Syndrome Due to Occlusion of All Arteries Arising from the Aortic Arch, *Am. Heart J.* **22**:825 (Dec.) 1941.

67. McLaughlin, C. W.: Postoperative Gangrene of the Finger Following Digital Nerve Block Anesthesia, *Am. J. Surg.* **55**:588 (March) 1942.

68. Perner, L.: Gangrene of the Toe, Following Local Anesthesia with Procaine-Epinephrine Solution, *New York State J. Med.* **42**:544 (March 15) 1942.

69. Heller, G., and Alvari, G.: Gangrene of the Extremities in the Newborn, *Am. J. Dis. Child.* **62**:133 (July) 1941.

70. Davies, J. N. P., and Hewer, T. F.: Ainhum: Report of a Case in England with Histological Study, *Tr. Roy. Soc. Trop. Med. & Hyg.* **35**:125 (Sept.) 1941.

vascular disease and intermittent claudication, but histologic study demonstrated that the changes in the little toes were of local origin and in no way suggestive of arteriosclerotic gangrene. The authors suggest that epidermophytosis might lead to such lesions, even though no fungus could be demonstrated in this case.

#### THROMBOANGIITIS OBLITERANS

Thompson<sup>71</sup> stresses the relation of dermatomycosis not only to thromboangiitis obliterans but to thrombophlebitis, phlegmasia alba dolens, migratory phlebitis and postphlebotic ulcer. Rather than consider a superficial mycosis as being merely incidental, the author has reason to believe that this infection may play a more vital role, possibly providing the etiologic agent for the vascular disorder itself. Even though there is no evidence to incriminate fungi directly, the vessels and deeper tissues may react in a manner similar to the well recognized allergic reaction of tissue elsewhere to the products of these organisms. As examples, reference is made to the dermatophytid and the characteristic "tuberculin type of reaction."

Naide<sup>72</sup> also shares this opinion with Thompson. Of his series of 30 patients with thromboangiitis obliterans, 28 (93 per cent) had dermatophytosis clinically, severe in 20. Of 30 controls, men between the ages of 20 and 50 without thromboangiitis obliterans, 22 (73 per cent) had dermatophytosis clinically, severe in 9. Vesicles, extensive scaling, fissures and involvement of nails were definitely more common among patients with thromboangiitis obliterans than among the controls. On microscopic examination fungi were found in 5 to 12 patients with Buerger's disease, a proportion usually obtained in all patients with dermatophytosis. The trichophytin test was also revealing. Cutaneous tests were made with trichophytin (1:30) on 30 patients with thromboangiitis obliterans. After forty-eight hours 24 patients (80 per cent) gave positive reactions to trichophytin. Of the 30 controls, 6 (20 per cent) gave positive reactions. Of the 8 controls without clinical evidence of dermatophytosis, none gave a positive reaction.

Ten of the patients were observed during attacks of migratory phlebitis. Seven of these had an exacerbation of dermatophytosis preceding the attack of phlebitis. The author is in agreement with Thompson that the evidence to date is insufficient to suggest an etiologic relation between the two diseases, but he believes that certain clinical features of thromboangiitis obliterans are more readily accounted for

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71. Thompson, K. W.: The Relationship of the Dermatomycoses to Certain Peripheral Vascular Infections, *Internat. Clin.* 2:156 (June) 1941.

72. Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans, *Am. J. M. Sc.* 202:822 (Dec.) 1941.

on the basis of fungous infection than by other etiologic mechanisms thus far proposed. This theory should not be disregarded, but additional study is necessary before acceptance.

That cardiac disease is not uncommon in patients with thromboangiitis obliterans has apparently been well established. On the other hand, surprisingly few cases of coronary thrombosis secondary to this disease have been reported. A case of such an occurrence was recently submitted by Greenfield,<sup>73</sup> but since the patient in this case survived, definite pathologic proof is lacking. From the literature cited by Greenfield one wonders if the incidence of involvement of the coronary arteries is as great as previously considered.

No mention is made of the possibility of coexisting arteriosclerosis, as many patients with Buerger's disease live sufficiently long for degenerative changes to develop. It is our opinion that changes in the electrocardiograms of patients with long-standing thromboangiitis obliterans are, in many instances, secondary to coronary sclerosis. The possibility of arterial disease predisposing one to arteriosclerosis must also be considered.

On reporting 4 cases of thromboangiitis obliterans involving the arteries of the brain, Antoni<sup>74</sup> suggested that this condition might be more common than previously considered, as in many cases the condition has undoubtedly been given the incorrect diagnosis of juvenile arteriosclerosis.

Three cases were presented by Silbert<sup>75</sup> in which thromboangiitis obliterans and polycythemia occurred in association in the same patient. This combination is so rare that Silbert considered it coincidental. Fatherree and Hurst<sup>76</sup> report the association of thromboangiitis with scleroderma. This combination was not only unusual in itself but of interest in that the scleroderma developed after cervicothoracic sympathectomy.

Thromboangiitis in Negroes is probably more common than the literature leads one to believe. A case was recently reported by Warshawsky.<sup>77</sup>

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73. Greenfield, I.: Coronary Artery Thrombosis, with Recovery, in a Case of Thromboangiitis Obliterans, *Am. Heart J.* **22**:707 (Nov.) 1941.

74. Antoni, N.: Buerger's Disease, Thrombo-Angiitis Obliterans, in the Brain: Report of Four Cases, *Acta med. Scandinav.* **108**:502 (Oct.) 1941.

75. Silbert, S.: Thrombo-Angiitis Obliterans and Polycythemia Vera, *J. Mt. Sinai Hosp.* **8**:1021 (Jan.-Feb.) 1942.

76. Fatherree, T. J., and Hurst, C.: Thromboangiitis Obliterans and Acrosclerosis, *Northwest Med.* **40**:200 (June) 1941.

77. Warshawsky, H.: Thromboangiitis Obliterans in the Negro: Report of a Case, *M. Bull. Vet. Admin.* **18**:83 (July) 1941.

## PERIARTERITIS NODOSA

Twenty additional cases of periarteritis nodosa were reported during the past year.<sup>78</sup> The numerous articles on this disease have undoubtedly made clinicians more conscious of its occurrence, resulting in more frequent diagnosis. Felsen made the diagnosis in 1 case prior to death by a sigmoidoscopic study. He noted peculiar horizontal linear dark red streaks running in parallel lines in the rectosigmoid area. Careful study with a telescopic device revealed that these lesions were within the vessels and that the widened areas within the vessels were thrombotic. Subsequent study at autopsy confirmed his observations.

## TEMPORAL ARTERITIS

Four cases of temporal arteritis were reported this year.<sup>79</sup> No new comment was made on the causation or on the characteristics of the pathologic picture.

Gilmour<sup>80</sup> cites 4 cases of a rare and little known form of arteritis. Syphilis was excluded in 3 of his cases, and in most of those reported in the literature. Tuberculosis is also excluded. The essential microscopic change is inflammation, and the prodromal symptoms are strongly suggestive of infection. The microscopic and the clinical features do not resemble those encountered in other types of arteritis. The author believes that the disease is probably a separate entity. In the branches of the arch of the aorta and in the internal and the external carotid

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78. Keith, H. M., and Baggenstoss, A. H.: Primary Arteritis (Periarteritis Nodosa) Among Children, *Proc. Staff Meet., Mayo Clin.* **16**:568 (Sept. 3) 1941. Blaisdell, E. R., and Porter, J. E.: Healed Stage of Periarteritis Nodosa: Report of Case, *New England J. Med.* **224**:1087 (June 26) 1941. Foster, D. B., and Malamud, N.: Periarteritis Nodosa, *Univ. Hosp. Bull., Ann Arbor* **7**:102 (Dec.) 1941. Jones, G. M.: Periarteritis Nodosa, with Case Reports, *Ann. Int. Med.* **16**:920 (May) 1942. Stewart, A. M.: Periarteritis Nodosa, *Proc. Roy. Soc. Med.* **35**:18 (Nov.) 1941. Malamud, N., and Foster, D. B.: Periarteritis Nodosa, *Arch. Neurol. & Psychiat.* **47**:828 (May) 1942. Spalding, J. E.: Periarteritis Nodosa and Its Surgical Significance: Report of a Case, *Guy's Hosp. Rep.* **90**:234, 1940-1941. Maxwell, E. S., and Maxson, W. T.: Cerebral Type of Periarteritis Nodosa: Case Report, *Internat. Clin.* **2**:217 (June) 1941. Williams, R. R., and Zeek, P.: Periarteritis Nodosa with Peripheral Polyneuritis and Hyperglycemia, *Ohio State M. J.* **38**:148 (Feb.) 1942. Lund, H. Z.: Periarteritis Nodosa, *ibid.* **38**:244 (March) 1942. Coe, M.; Reisman, H. A., and DeHoff, J.: Periarteritis Nodosa in a Nine-Year-Old Child, *J. Pediat.* **18**:793 (June) 1941. Felsen, J.: The Sigmoidoscopic Diagnosis of Periarteritis Nodosa, *Ann. Int. Med.* **15**:251 (Aug.) 1941.

79. Hoyt, L. H.; Perera, G. A., and Kauvar, A. J.: Temporal Arteritis, *New England J. Med.* **225**:283 (Aug. 21) 1941. Scott, T., and Maxwell, E. S.: Temporal Arteritis: A Case Report, *Internat. Clin.* **2**:220 (June) 1941.

80. Gilmour, J. R.: Giant-Cell Chronic Arteritis, *J. Path. & Bact.* **53**:263 (Sept.) 1941.

artery the disease is focal, bilateral and symmetric, while in the aorta it is usually widespread. The inflammation apparently heals in time, but death has occurred from rupture of an aneurysm or from thrombosis during active inflammation. Multinuclear giant cells are present in most of the affected vessels, and consequently the author gives this disease the name of giant cell chronic arteritis.

Neel and Herrmann<sup>81</sup> report a case of sudden occlusion of the major vessels to the left leg by a large embolus originating in an area of tuberculous thrombophlebitis of the pulmonary vessels. This was confirmed at autopsy, but of interest were the associated metastatic foci of tuberculous arteritis.

Fite<sup>82</sup> noted that in the cutaneous lesions in 32 of 77 cases of leprosy, some involvement of the blood vessels was present, usually with bacilli in the lining of endothelial cells. Infection of the terminal vascular loop was the most common occurrence, whereas the larger vessels were involved in a variety of ways. Arteries and veins were involved with equal frequency.

#### VASCULAR TUMORS

Thirteen cases of glomus tumors were reported during the last year.<sup>83</sup> Of interest were the 4 cases collected by Kaufman and Clark from the same family.

Thomas<sup>84</sup> reports on the pathologic and clinical analysis of 27 cases of benign and of malignant vascular tumors involving bone. This study was made possible through the cooperation of the Bone Sarcoma Registry of the American College of Surgeons, proving the value of

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81. Neel, W., and Herrmann, L. G.: Tuberculous Peripheral Arteritis Associated with Tuberculous Thrombophlebitis in the Lungs, *Am. Heart J.* **22**:702 (Nov.) 1941.

82. Fite, G. L.: The Vascular Lesions of Leprosy, *Internat. J. Leprosy* **9**:193 (April-June) 1941.

83. Kaufman, L. R., and Clark, W. T.: Glomus Tumors, *Ann. Surg.* **114**: 1102 (Dec.) 1941. Jaeger, J. R., and Kingry, C. B.: Glomus Tumor, *Rocky Mountain M. J.* **38**:717 (Sept.) 1941. Monserrat, J. L.: Tumor glómico de la concha del pabellón auricular, *Rev. argent. de oto-rino-laring.* **9**:173 (May-June) 1940. Milch, H.: Pressure Atrophy of Terminal Phalanx Due to Subungual Glomus, *Bull. Hosp. Joint Dis.* **2**:128 (July) 1941. Beaton, L. E., and Davis, L.: Glomus Tumor: Report of Three Cases; Analysis of Two Hundred and Seventy-Four Reported Cases, *Quart. Bull. Northwestern Univ. M. School* **15**:245, 1941. Murray, M. R., and Stout, A. P.: The Glomus Tumor, *Am. J. Path.* **18**:183 (March) 1942. Loeb, M. J.: Trauma and Glomus Tumors, *Indust. Med.* **10**: 208 (May) 1941. Rypins, E. L.: The Roentgenologic Aspects of Subungual Glomus Tumor, *Am. J. Roentgenol.* **46**:667 (Nov.) 1941.

84. Thomas, A.: Vascular Tumors of Bone: A Pathological and Clinical Study of Twenty-Seven Cases, *Surg., Gynec. & Obst.* **74**:777 (April) 1942.



such a registry for studying rare conditions. All of the tumors were true endotheliomas, mesenchymal in type, arising from congenital rests by a process of endothelial proliferation and differentiation into new blood vessels. The typical benign angioma is a highly differential structure composed of fully developed blood vessels which grows slowly and with little evidence of cellular activity. As the symptoms are not pathognomonic the diagnosis is usually established by roentgen examination. The characteristic roentgenograms vary depending on whether vertebrae or flat or long bones are involved. Treatment is quite successful by irradiation or operation or both.

The malignant angiomas are characterized by rapid growth, invasion of surrounding tissue and sometimes metastasis. They consist of highly cellular angioblastic tissue, which in its histogenesis tends to revert to the original primitive mesenchymal structure, producing a varied histologic picture differing greatly from the well differentiated benign forms. There is always present an angioblastic tendency evidenced by endothelial proliferation and the formation of new blood vessels. Diagnosis is difficult, as malignant angiomas possess few characteristic roentgenographic or clinical features. Diagnosis is based largely on their histologic appearance. They are only moderately radiosensitive, and early diagnosis and radical surgical treatment are essential for cure.

Four cases of venous angioma of skeletal muscle were reported by Fulton and Sosman.<sup>85</sup> In these cases the diagnosis was made by the roentgen demonstration of phleboliths in the tumor. The authors believe that the finding of multiple phleboliths in areas of the body where normally no plexus of veins exists is practically pathognomonic of a venous angioma. This is particularly true in the extremities.

#### EDEMA

The mechanism of edema formation in failure of the right side of the heart was studied by Fahr and Ershler.<sup>86</sup> It was found to be due to the rise in capillary hydrostatic pressure rather than to anoxemia. Edema develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm. or less of the colloid osmotic pressure. This is particularly true if a patient is up and about, if no precautions are taken as to salt and water restriction and if no diuretics are given. When the colloid osmotic pressure is normal, 22 mm. of mercury, a tendency toward edema is present when the hydrostatic pressure in the venous end of the capillaries is 20 mm. of mercury or

85. Fulton, M. N., and Sosman, M. C.: Venous Angiomas of Skeletal Muscle, *J. A. M. A.* **119**:319 (May 23) 1942.

86. Fahr, G., and Ershler, I.: Studies of the Factors Concerned in Edema Formation: II. The Hydrostatic Pressure in the Capillaries During Edema Formation in Right Heart Failure, *Ann. Int. Med.* **15**:798 (Nov.) 1941.

the venous pressure in the arm veins is 13 mm. of mercury. A drop in colloid osmotic pressure of 7 mm. of mercury or a rise in capillary pressure of 8 mm. of mercury produces approximately the same tendency toward edema. A tendency toward edema is also present when the colloid osmotic pressure is not more than 9 mm. higher than the venous pressure in the arm.

A case of unilateral hypertrophy of the leg due to venous retardation was described by Luke.<sup>87</sup> A thorough study was made as to the cause of this enlargement, as it resembled clinically an instance of venous congestion. In this case the patient had been previously healthy and gave no history of phlebitis. There was no evidence of lymphatic blockage. The diagnosis was finally established by roentgenograms made after the injection of diodrast. This study revealed the absence of, or defective valves in, the deep venous system of the involved leg. The author considered that venous pressure caused the hypertrophy of the leg. Apparently this extremity was endowed with a set of valves congenitally weaker or numerically fewer than normal.

#### TREATMENT

Assuming that an increase in blood volume should benefit patients with deficient circulation led Hayward<sup>88</sup> to investigate the possibility of intravenous administration of serum in the treatment of peripheral vascular disease. Fifty transfusions were given to 16 patients suffering from a variety of peripheral vascular disorders, mainly of the occlusive type. Each transfusion consisted of 800 cc. of pooled liquid serum having a protein content of 7 per cent. Reactions were few, although chills and fever occurred on fifteen occasions. After transfusion the blood volume increased markedly, gradually returning to normal after two to three days. The oscillometric readings and cutaneous temperatures apparently increased. The response to reflex vasodilatation was greater after transfusion than before. The results of these special studies are not clear. As an example, the serum did not increase the surface temperature if the skin was cold but did so if the skin was warm. In 3 patients the reflex method of producing vasodilation failed to produce a response prior to the administration of serum, whereas after serum was given a normal response was elicited. One questions the technic,

The clinical results were good. In all, 7 of 10 patients with cold limbs had improvement in the warmth of the limb; in the remaining 3 there was little increase in warmth. Of the 8 patients with pain at

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87. Luke, J. C.: The Diagnosis of Chronic Enlargement of the Leg, with the Description of a New Syndrome, *Surg., Gynec. & Obst.* **73**:472 (Oct.) 1941.

88. Hayward, G. W.: Intravenous Serum in the Treatment of Peripheral Vascular Disease, *Brit. M. J.* **1**:285 (Feb. 28) 1942.

rest, all were relieved; in 6 it was complete after the first transfusion and in 2 only after three transfusions. The walking distance of 4 of 6 patients with intermittent claudication was improved. One of the 3 patients with Raynaud's disease improved. Pregangrenous color changes improved in 4 patients. All of the 6 patients with ulcers of limbs associated with chronic arterial disease recovered after one to three transfusions.

The author was of the opinion that the action of intravenously administered serum was purely mechanical, produced by the increase in blood volume which follows the transfusion.

Linton and his associates,<sup>89</sup> using a perfected thermostromuhr, presented laboratory evidence that therapeutic venous occlusion increased the arterial blood flow to the hind extremity of dogs. The increased flow occurs during the time of occlusion but returns to normal when the pressure is released. A pneumatic tourniquet produces a greater inflow of blood than ligation of the main vein from the leg. The increase in blood flow appears to be directly related to the height of the venous pressure up to a certain level, above which the arterial inflow begins to decrease. These results were obtained with patent, as well as occluded, arteries, although in the latter the maximum flow occurred much less rapidly. As the flow increased only during the period of venous occlusion, the authors are of the opinion that in the treatment of arterial occlusion by intermittent venous congestion the period of venous obstruction should be longer than the period of release. By studying the blood flow in one extremity while venous occlusion was produced in the contralateral one, it was shown that the increase in the arterial blood flow is probably not caused by a humoral or a nervous mechanism. The authors expressed the opinion that a mechanical dilatation was the most likely explanation for this phenomenon.

Horton, Krusen and Sheard<sup>90</sup> studied the effect of various mechanical devices currently used in the treatment of peripheral vascular diseases on the surface temperatures of the toes. Normal subjects, as well as patients with peripheral vascular diseases, were used in their experiments. From their results they concluded that neither the pavaex machine nor apparatus for intermittent venous occlusion is capable of promoting increased blood flow in normal extremities or of value in treating persons with peripheral vascular disease. The best results were obtained by the use of an oscillating bed, provided that this is

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89. Linton, R. R.; Morrison, P. J.; Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion: Its Effect on the Arterial Inflow to an Extremity, as Measured by Means of the Rein Thermostromuhr, *Am. Heart J.* **21**:721 (June) 1941.

90. Horton, B. T.; Krusen, F. H., and Sheard, C.: An Evaluation of Methods and Mechanical Devices Used in the Treatment of Peripheral Vascular Diseases, *Arch. Phys. Therapy* **22**:389 (July) 1941.

used in an environmental temperature of 85 to 87 F. (29.5 to 30.5 C.), at which level vasospasm ceases to exist. It must be remembered that this evaluation depended solely on the assumption that surface temperature is an index of blood supply.

A similar evaluation of the usefulness of various physical measures in the treatment of peripheral vascular diseases was presented by Wright.<sup>91</sup> Practically all of the therapeutic agents employed at present are mentioned, with particular emphasis on their indications and contraindications. No specific data are given on the results obtained, but favorable comment is made on agents producing heat, active vascular exercises, the oscillating bed and iontophoresis employing acetyl-beta-methylcholine. Wright was not convinced of the value of intermittent venous occlusion and, to a lesser degree, the pressure suction boot.

The vasodilating action of a number of procedures used in the treatment of peripheral vascular diseases was investigated by Abramson, Zazeela and Schkloven<sup>92</sup> by means of the venous occlusion plethysmograph. Studies were done on a series of normal patients, patients with peripheral circulatory disease and patients with various mental states. A single administration of calcium gluconate; a deproteinized pancreatic extract (padutin); papaverine hydrochloride; a mixture of atropine, hydrochlorides of opium alkaloids and papaverine (spasmalgin), and thiamine hydrochloride produces only a slight increase or none at all in the blood flow to the hand, the forearm, the leg and the foot. Alcohol, diethylstilbestrol and histamine acid phosphate generally increase the blood flow to the hand but not to any other portion of the extremities. Hypertonic solution of sodium chloride produces an augmentation of the flow to the hand, leg and foot in a third of the trials. The application of a venous occlusion pressure for two or three hours does not produce a significant increase in peripheral blood flow. The authors also presented evidence by their method of study that results of surface temperature studies and oscillometric readings do not necessarily reflect or parallel changes in total blood flow to an extremity. It is our opinion that the data obtained in these experiments are parallel in part to the clinical results obtained from the use of these procedures. This paper also serves to emphasize the need for more thorough investigation of new therapeutic procedures before they are accepted.

Interest is being aroused on the question of heat versus cold in the treatment of certain types of peripheral vascular diseases. The

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91. Wright, I. S.: Physical Measures in the Treatment of Peripheral Vascular Disease, *J. Mt. Sinai Hosp.* 8:1128 (Jan.-Feb.) 1942.

92. Abramson, D. I.; Zazeela, H., and Schkloven, N.: The Vasodilating Action of Various Therapeutic Procedures Which Are Used in the Treatment of Peripheral Vascular Disease, *Am. Heart J.* 21:756 (June) 1941.

previously reviewed work by Allen and his associates on the use of refrigeration as a preliminary to amputation in older patients appears to be gaining favor. Its use in younger persons has recently been suggested by Ochsner,<sup>93</sup> especially in those in whom there is interference with the blood supply as a result of trauma. He suggested that the associated vasospasm be controlled by injection of the sympathetic ganglions with procaine hydrochloride or alcohol. To us the question is not entirely one of controlling the associated vasospasm. It is doubtful if blocking the ganglions will prevent the local action of cold on the vessels anyway. The question is, does collateral circulation develop with the correct amount of refrigeration in these patients or does the cold produce an unchanging condition in the extremity in which neither gangrene nor collateral circulation develops? Many of the details of this form of therapy remain obscure, and consequently more investigation is needed before adoption.

Stein and Weinstein<sup>94</sup> studied the effect of carbon dioxide baths on the peripheral circulation. European authors previously demonstrated that carbon dioxide diffuses through the dermal layers, thus coming into contact with the network of small blood vessels and causing them to dilate. The resultant hyperemia is usually localized to the contact area and is unaccompanied by an appreciable rise in tissue or general metabolism. The authors studied a series of patients submitted to these baths. In all of the subjects the cutaneous temperature increased during the treatment and decreased gradually afterward. When tap water was substituted, the results were similar except that the temperature of the skin fell more rapidly after the completion of the treatment. Capillary studies and blood flow measurements were also made. Blood flow was increased, and in the capillary studies an extraordinarily large number of capillary tufts and loops became visible after exposure. The authors suggest the clinical application of this process but do not report any of their results. One wonders if this is an attempt to resurrect the spa treatments of continental Europe.

Fatherree and Hurst<sup>95</sup> report their observations at Soap Lake, Wash., recently popularized as a spa beneficial to patients with thromboangiitis obliterans. A statistical analysis of 32 patients was made, including not only the usual data but the progress of the disease before and during residence in this area. The apparent popularity of Soap

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93. Ochsner, A.: The Use of Refrigeration Combined with Vasodilatation to Preserve Vitality in a Relatively Ischemic Extremity, *Surgery* **11**:819 (May) 1942.

94. Stein, I. D., and Weinstein, I.: The Value of Carbon Dioxide Baths in the Treatment of Peripheral Vascular Disease and Allied Conditions, *Am. Heart J.* **23**:349 (March) 1942.

95. Fatherree, T. J., and Hurst, C.: The Spa Treatment of Thromboangiitis Obliterans, *Am. Heart J.* **22**:180 (Aug.) 1941.

Lake lies in the considerable percentage of gangrenous and ulcerative lesions which heal while the patients are treating themselves in this lake. The authors are of the opinion that the frequent healing of these lesions was not due to the water but occurred because the gangrenous extremities were kept at rest, kept clean and not subjected to meddlesome surgical procedures.

The dietary history and clinical data for 21 patients with Raynaud's syndrome are reported by Spiegel.<sup>96</sup> In most patients the history revealed a deficient intake of vitamins, and in a few clinical avitaminosis was present. These patients were treated for six weeks to one year either with "total vitamins" or with vitamin B complex. Fifteen showed distinct relief from attacks of vascular spasm. Three remained asymptomatic and are being maintained on a normal diet. The vitamin B complex appears to be the effective therapeutic group of vitamins. The authors were unable to determine which was the essential specific factor. When thiamine hydrochloride and pyridoxine were used individually they were ineffective. Thiamine hydrochloride and pyridoxine in large doses actually caused exacerbation of symptoms in patients who had previously improved under vitamin B therapy. Apparently the several components of the vitamin B complex are necessary, although no relation between this deficiency and the pathologic mechanism of Raynaud's syndrome could be adequately explained.

King<sup>97</sup> successfully treated 10 patients with thromboangiitis obliterans with deproteinized pancreatic extract. In all cases relief from intermittent claudication and pain at rest was noted. The subjects studied probably had arteriosclerosis obliterans rather than thromboangiitis obliterans.

Davidson<sup>98</sup> successfully treated 3 patients with septic thrombophlebitis with heparin and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). The usual dose of each drug was used.

#### ABNORMALITIES OF BLOOD PRESSURE

Kean<sup>99</sup> studied blood pressure in West Indians and Panamanians in an effort to add to the information regarding the relation of race and climate to variations in blood pressure. He discusses observations made in many previous reports, some of which are controversial. It has been believed that blood pressure in persons living in the tropics

96. Spiegel, R.: Vitamin Therapy in Raynaud's Disease, *J. Mt. Sinai Hosp.* 8:284 (Nov.-Dec.) 1941.

97. King, G. S.: Deproteinized Pancreatic Acid: Use in Thromboangiitis Obliterans, *Indust. Med.* 10:530 (Dec.) 1941.

98. Davidson, H. S.: The Treatment of Septic Thrombophlebitis with Heparin and Sulfathiazole, *J. M. Soc. New Jersey* 38:642 (Dec.) 1941.

99. Kean, B. H.: Blood Pressure Studies on West Indians and Panamanians Living on the Isthmus of Panama, *Arch. Int. Med.* 68:466 (Sept.) 1941.

is low and that hypertension is not common among them. It is said to be rare among the Chinese and in Australian aborigines. The incidence in American Negroes is high, while blood pressure in Negroes living under primitive conditions in Africa is cited as being similar to that in white persons up to the age of 40 and after this age averaging less than that in white persons.

Kean's own studies were conducted on native Panamanians and West Indians living on the Isthmus of Panama. The incidence of increased blood pressure was much greater in the West Indians than in the native Panamanians. The converse was true for low blood pressure. The average of blood pressures taken was higher for the West Indian group, and the incidence of hypertension was actually greater in this group as well.

It would be of considerable interest to follow up this work with blood pressure studies on West Indians in their home environment. The impression is prevalent that the existence of hypertension and vascular diseases in general is high in the American Negro population. This is quite in contrast to observations made on aboriginal Negroes. To speculate on the factors causing this is, of course, futile, but the question of the effect of change of environment to a cold climate on a vascular system adjusted through generations of life in the tropics is interesting and perhaps important. This may be the reason for the supposed inferior vascular system of the American Negro.

*Cold Pressor Phenomena.*—The fact that the cold pressor phenomenon in hypertension is dependent on intact peripheral sensation was demonstrated by observations made by Sullivan<sup>100</sup> on a patient with a transection syndrome of fourteen years' duration. The spinal cord had been removed below the level of the first lumbar segment, with complete motor and sensory paralysis. The circulation of the blood in the legs was unimpaired.

When either hand was immersed in ice water a constant rise in blood pressure was noted, from 120 to 140 systolic and from 90 to 104 diastolic on one occasion. An increase in heart rate accompanied this rise in pressure. When a foot was immersed, no constant change was noted either in systolic or in diastolic pressure. This observation substantiates the assumption that the cold pressor response is due to a reflex, resulting from sudden stimulation of the cutaneous nerve endings for pain and temperature sense.

Feldt and Wenstrand<sup>101</sup> have made a comparison of the results of the cold pressor test and the breath-holding test as a stimulus for the

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100. Sullivan, J. D.: Dependence of Cold Pressor Reaction on Peripheral Sensation, *J. A. M. A.* **117**:1090 (Sept. 27) 1941.

101. Feldt, R. H., and Wenstrand, E. E. W.: The Cold Pressor and Breath Holding Test: An Analysis of Results in Two Hundred Subjects, *Arch. Int. Med.* **67**:1157 (June) 1941.

detection of persons who respond with an excessive rise in blood pressure. Both tests were made on 200 persons with normal and with elevated pressure.

Both procedures were found to produce a rise in blood pressure. Statistically, the response was similar except in one classification. Among normal hyporeactors to the two tests the systolic response to the breath-holding test greatly exceeded the response to the cold pressor test. In most of the subjects the response to the cold pressor test was the same or higher than the response to breath holding. Wide differences were sometimes encountered in the same person. Hyper-reaction to cold was observed in 39 persons who reacted normally to breath holding, while in 16 persons the opposite was noted.

While the arithmetical mean results correspond well, the individual differences seem to be too great to indicate that the results can be regarded as showing "striking similarity."

Abramson and Fierst<sup>14</sup> have made observations on blood flow in the forearm, the leg and the hand in hypertensive subjects at rest. Blood flow in the forearm and in the leg was found to be considerably higher in hypertensive subjects than in normal persons. In the hand, on the contrary, blood flow was found to be uniformly less in the hypertensive subjects than in the normal ones, in striking contrast to the results obtained in the forearm and the leg.

When the blood flow was correlated with the height of the blood pressure, it was observed that there was a marked relation between the forearm flow and both systolic and diastolic levels.

From their data the authors conclude that the theory of general and uniformly increased peripheral resistance to blood flow in hypertensive persons cannot be held in view of their observations that blood flow is not the same throughout the body. If the increased resistance is localized, then it might be expected that a more rapid rate of flow would exist in those parts of the body in which the resistance was not increased.

There is, of course, considerable variation of opinion in this respect, and as the authors point out, it cannot be stated that the augmented blood flow through the leg and the forearm is the result solely of an increase in tone of the vascular bed in other parts. Further studies will be necessary to decide this matter ultimately.

The relation of pregnancy and toxemias of pregnancy to later hypertension in women has been the subject of several papers.

A follow-up study<sup>102</sup> of 167 eclamptic women was made. In 147 survivors the incidence of subsequent hypertension was 17.5 per cent.

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102. Chesley, L. C., and Somers, W. H.: Eclampsia and Post Eclamptic Hypertension: Follow Up Study with Analysis of Factors Effecting Remote Prognosis, Surg., Gynec. & Obst. **72**:872 (May) 1941.



Proteinuria occurred in 2.6 per cent. Renal function as usually measured was within the normal range in 97 per cent. The majority had changes in the fundi of significant type, and one half of them had cardiac enlargement. Hypertension was more likely if there had been antecedent renal disease, elevated blood pressure during pregnancy, many previous children or long and severe eclampsia.

Williams, Nix and Manzy<sup>103</sup> in a follow-up study of 224 women with toxemia of pregnancy found that 80 per cent of those above 35 years of age had blood pressures in excess of 140 systolic and 90 diastolic. The severity and the type of toxemia seemed to have no special relation in those who did not have previous hypertension or nephritis. Later hypertension was much more frequent in those who had had toxemia and subsequently had a later pregnancy than in those who had only one pregnancy.

In another statistical study on the subject Isenhour, Kuder and Dill<sup>104</sup> found that the incidence of hypertension both in parous and in nulliparous women was above the average usually stated as normal for men. They believe that it is reasonable to suppose that the vascular system of the female has an increased tendency toward hypertension. This does not seem to be actually demonstrable.

They conclude that there is no relation between hypertension and pregnancy itself and that hypertension and "hypertension-producing" diseases which occur after a large proportion of toxemias of pregnancy are due to defects in the vascular systems of the persons affected which predispose them to both the toxemias of pregnancy and hypertension.

It is apparent that while there is some disagreement in detail, still there is a definite increased frequency of hypertension following this complication of pregnancy, whether it bears a causal relation or whether both conditions have a common underlying cause.

The exact nature of experimental hypertension produced by constriction of the renal artery or by compression of the kidney itself is still under discussion. The similarities to and differences from hypertension in human beings have brought forth efforts both clinical and experimental to link the two forms together and thus place essential hypertension in the classification of renal diseases. Certainly it must be admitted that the numerous counterparts of experimental hypertension encountered in human beings furnish evidence enough to warrant careful investigation of every clinical case showing the symptom com-

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103. Williams, T. J.; Nix, H. G., and Manzy, C. H.: The Incidence of Hypertension After the Toxemias of Pregnancy, *Am. J. Obst. & Gynec.* **42**:98 (July) 1941.

104. Isenhour, C. E.; Kuder, K., and Dill, L. V.: The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension, *Am. J. M. Sc.* **203**:333 (March) 1942.

plex of hypertension. Certainly the separation and grouping of cases showing increased blood pressure is important for no other reasons than those of prognosis and diagnosis, and therefore treatment in some cases.

Schroeder and Steele<sup>105</sup> have continued their clinical studies on hypertension and point out that the identity of essential hypertension has been seriously called into question. They note that chronic bilateral pyelonephritis is now recognized as a cause for the rise in pressure and have therefore investigated a number of other renal abnormalities which they consider to have some significance in this respect.

They studied 250 cases for the purpose of discovering some associated renal disease. Some type of renal disease was encountered in 113. The onset of such disease often occurs much earlier than the development of hypertension, and while the disease itself may be one not usually associated with it, yet the frequency with which renal disease occurs suggests that it may be at least a factor in the genesis of hypertension. Another, according to the authors, may be an inherited predisposition shown in the quality of the vascular system which is responsible for the cold pressor reaction.

Prinzmetal, Hiatt and Tragerman<sup>106</sup> report a case of bilateral infarction of the renal arteries which appeared at autopsy to produce bilateral obstruction of these arteries exactly similar to that produced experimentally by Goldblatt. There was a well marked rise in blood pressure within a few days. The case is a perfect example of acute renal ischemia in a human being. Perfusates of the kidney had the same hypertensive properties as do those of experimental animals. Hypertension following thrombosis of the renal veins has also been reported.<sup>107</sup>

Braasch and Wood<sup>108</sup> encountered 3 instances of hypertension in a group of 70 cases of perinephritis or perinephritic abscess. In these instances it was impossible for the authors to draw any conclusion as to a causal relation to constriction or compression of the kidney.

Baggenstoss and Barker<sup>109</sup> studied a group of cases of unilateral renal atrophy and observed that hypertension was somewhat more fre-

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105. Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: II. The Association of Hypertension with Organic Renal Disease, *Arch. Int. Med.* **68**:261 (Aug.) 1941.

106. Prinzmetal, M.; Hiatt, N., and Tragerman, L.: Hypertension in Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, *J. A. M. A.* **118**:44 (Jan. 3) 1942.

107. Perry, C. B., and Taylor, A. L.: Hypertension Following Thrombosis of Renal Veins, *J. Path. & Bact.* **51**:369 (Nov.) 1940.

108. Braasch, W. F., and Wood, W. W., Jr.: Clinical Perinephritis and Blood Pressure, *Proc. Staff Meet., Mayo Clin.* **52**:54 (Jan. 28) 1942.

109. Baggenstoss, A. H., and Barker, N. W.: Unilateral Renal Atrophy Associated with Hypertension, *Proc. Staff Meet., Mayo Clin.* **16**:833 (Dec. 31) 1941.

quent in their group than could be expected had it occurred only by chance. Increased blood pressure is more likely to be associated if the degree of atrophy is severe. The causes of atrophy were pyelonephritis and hydronephrosis in most instances.

In confirmation of the present state of awareness of the relation between hypertension and renal disease are the large number of individual case reports and extended studies of unilateral renal disease of urologic type in which hypertension is considered a relevant factor.

Reports on cases of juvenile hypertension are increasing in number doubtless because blood pressure observations are now being made on children much more frequently than in years past. Killian and Calvin<sup>110</sup> reported 6 cases of persistent hypertension in children from 4½ to 14 years of age. The hypertension was of renal origin in all cases in only 1 of which the renal disorder was subacute glomerulonephritis. Pyelonephritis, hydronephrosis and congenital unilateral hypoplasia of the kidney made up the balance. The authors note that hypertension may occur much more frequently in childhood than is often suspected.

Powers and Murray<sup>111</sup> have reported 1 case of juvenile hypertension due to pyelonephritis and aplasia of one kidney successfully treated by surgical intervention and have reviewed 14 cases previously reported. The renal lesions in these cases have been classified as neoplastic, obstructive, congenital and inflammatory.

Kimmel's<sup>112</sup> findings in regard to pyelonephritis reflect much the same viewpoint.

Benjamin and Ratner,<sup>113</sup> Court,<sup>114</sup> Toulson and Wagner<sup>115</sup> and Kerley and Lorenze<sup>116</sup> likewise report hypertension in infancy and childhood, in all instances either due to or associated with renal disease, most often pyelonephritis.

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110. Killian, S. T., and Calvin, J. K.: Renal Hypertension in Children, *Am. J. Dis. Child.* **62**:1242 (Dec.) 1941.

111. Powers, J. H., and Murray, M. F.: Juvenile Hypertension Associated with Unilateral Lesions of the Upper Urinary Tract, *J. A. M. A.* **118**:600 (Feb. 21) 1942.

112. Kimmel, G. C.: Hypertension and Pyelonephritis of Children, *Am. J. Dis. Child.* **63**:60 (Jan.) 1942.

113. Benjamin, B., and Ratner, M.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis, *Am. J. Dis. Child.* **61**:1051 (May) 1941.

114. Court, D.: Malignant Hypertension in Childhood, *Arch. Dis. Childhood* **16**:132 (June) 1941.

115. Toulson, W. H., and Wagner, J. A.: Congenital Encapsulated Multilocular Serous Cyst of the Kidney Associated with Hypertension: Occurrence in a Nineteen Months Old Infant; Report of Case, *Bull. School Med. Univ. Maryland* **26**:177 (Jan.) 1942.

116. Kerley, C. G., and Lorenze, E. J.: Blood Pressure Observations on Children in Private Practice, *J. Pediat.* **20**:383 (March) 1942.

## ENDOCRINE HYPERTENSION

The syndrome presented by tumors of the adrenal medulla has been reviewed in previous years. Additional case reports<sup>117</sup> appear frequently, and this disorder is apparently discovered often enough in an early stage to admit to successful surgical treatment.

Hantschmann<sup>118</sup> has, however, reported 5 cases of tumor involving the adrenal cortex associated with hypertension. In 4 of these biopsy or necropsy was done. In 3 cases the patients were women of middle age who showed hirsutism, facial rubor and reduced carbohydrate tolerance in addition to high blood pressure. Of the patients in the other 2 cases, both men, 1 had a hypernephroma and the other a cortical adenoma. Hantschmann believes the rise in blood pressure in these cases to be due to the secretion of a substance which is not epinephrine but related to it. In his opinion this substance has the ability to constrict the arterioles, but no capillary constriction occurs; hence the rubor. The symptoms are somewhat similar to those observed in adenomas of the anterior lobe of the pituitary. Further observations are clearly necessary to evaluate his data.

That chorionepithelioma may be accompanied by hypertension is shown by the reports of Adams.<sup>119</sup>

## EXPERIMENTAL HYPERTENSION

Page<sup>120</sup> has reviewed the status of experimental hypertension and presented the views which his extensive work on the subject permit him to form in regard to hypertension in human beings. As is well known, he places the emphasis on the theory of a humoral mechanism for the origin of the disorder and places the location of the effect in the afferent glomerular arteriole, although the essential alteration in the hemodynamics of the renal blood flow lies in the constriction of the efferent glomerular arteriole. He suggests that the process which

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117. Crane, J. J.; Alesen, L. A., and Touriel, E. L.: Tumor of the Suprarenal Medulla Associated with Paroxysmal Hypertension: Report of Case Preoperatively Diagnosed and Cured by Surgical Removal, *J. Urol.* **46**:100 (Dec.) 1941. Hamilton, J. E.: Pheochromocytoma of Adrenal with Paroxysmal Hypertension: Case Relieved by Surgery, *Kentucky M. J.* **38**:572 (Dec.) 1940. Allen, P. L.: Chromaffin Cell Tumor Associated with Paroxysmal Hypertension, *Texas State J. Med.* **36**:640 (Dec.) 1940.

118. Hantschmann, L.: Adrenal Cortex Tumors and Hypertension, *Klin. Wchnschr.* **20**:377 (April 19) 1941.

119. Adams, J. E.: A Study of Malignant Testicular Tumors Including Case Reports of Chorionepithelioma Accompanied by Hypertension, *J. Urol.* **47**:491 (April) 1942.

120. Page, I. H.: The Nature of Clinical and Experimental Arterial Hypertension, *J. Mt. Sinai Hosp.* **8**:3 (May-June) 1941; Arterial Hypertension, *J. Urol.* **46**:807 (Nov.) 1941.

initiates the disturbance in blood flow is probably arteriosclerosis, which may exist in this portion of the renal vascular structure alone. He discounts the effect of the central nervous system in the genesis of vascular hypertension and explains the results obtained by surgical extirpation of the sympathetic mechanism on the pooling of blood within the splanchnic vessels and diminished venous return to the heart which is most evident in the upright posture. Cardiac output is thus limited, and the peripheral pressure remains at a lower level as a consequence. So it may be said, if this is true, that such an operation does not alter the fundamental mechanism which is responsible for the genesis of the disorder in human beings.

The work of Corcoran and Page<sup>121</sup> on renal blood flow in experimental hypertension is comparable to that of other investigators. Renal blood flow is decreased in animals made hypertensive by compression of a renal artery if this compression has been marked or severe. These studies of Corcoran and Page were made on animals who were made hypertensive by only limited compression. Measurements of the renal blood flow calculated from the clearance of phenolsulfonphthalein and of inulin indicated that hypertension did exist without impairment of renal blood flow. Thus, renal ischemia is not essential to production of experimental hypertension. The essential mechanism is said to be intrarenal reduction of pulse pressure. That is, hypertension develops, or the humoral agent responsible for its development is released, as a consequence of the absence of pulsatile blood flow. Renal ischemia when present is then only an accompanying phenomenon. If this is true, the authors reason that the production of renin "must arise in some site normally exposed to high pulse pressure." Such a site must be proximal to the glomerulus and in close relation to the afferent arteriole. Surrounding or adjacent to these structures are groups of cells the nature or function of which is not well known. Because these cells are hypertrophied and show an increase in the number of their granules in animals with experimental hypertension, it has been assumed that they may be the site of the formation of renin.

In this paper a complete review of the subject of renal hemodynamics is discussed and developed in the logical fashion of the authors.

That sympathectomy, even the complete denervation operation of Smithwick, has no effect on renal blood flow as measured by the usual clearance methods was shown in 2 cases by Corcoran and Page.<sup>122</sup> The efferent arteriolar constriction was not reduced in either case studied. These observations corroborate ones made on animals with experimental hypertension. The authors repeat their view in regard

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121. Corcoran, A. C., and Page, I. H.: Renal Blood Flow in Experimental Renal Hypertension, *Am. J. Physiol.* **135**:361 (Jan.) 1942.

122. Corcoran, A. C., and Page, I. H.: Renal Aspects of Experimental and Clinical Hypertension, *J. Lab. & Clin. Med.* **26**:1713 (Aug.) 1941.

to the effect of sympathectomy being largely due to diminished cardiac output but suggest that the reduction of pressure in a hypertensive patient subjected to the operation may arrest the progress of renal arteriosclerosis and state:

Since these arteriolar lesions may contribute to the release of renin and the activity of the renal vasopressor system, sympathectomy may thus interrupt for a time the progress of the disease.

This would seem to be a compromise statement, which leaves the reader somewhat doubtful.

Friedman, Selzer and Rosenblum<sup>123</sup> are in essential agreement with Page in regard to the relation of renal ischemia to experimental hypertension. They likewise have found that it is not necessary for the initiation or maintenance of experimental hypertension.

Their observations were made on a group of hypertensive patients showing the disorder in varying grades of severity. They employed the usual clearance methods used for this purpose, including diodrast and inulin clearance. They found that in the majority of patients with hypertension effective renal blood flow was reduced somewhat, although glomerular filtration was approximately normal. The degree of elevation of diastolic pressure did have a direct bearing on the rate of blood flow and the glomerular filtration rate. It is interesting to note that observations on the group who showed intermittent or variable hypertension demonstrated that effective renal blood flow was normal in 2 patients who at the times of observation had normal diastolic blood pressures, but that in 2 others whose diastolic levels were only slightly elevated the flow was reduced.

They noted the increased tonus in the efferent glomerular arteriole and suggest that this represents

. . . the reflex or chemically motivated ability of these vessels to maintain an effective glomerular filtration pressure despite extra glomerular or intra glomerular hemodynamic changes, whether these changes were of pulse pressure or of blood flow.

The further suggestion is made that the efferent arteriolar constriction in itself initiates renal ischemia.

These observations are in essential agreement with those of Goldring, Chasis, Ranges and Smith,<sup>124</sup> who studied the same procedures in 60 cases of hypertension. They believe that the renal ischemia which is actually demonstrable, that is, constriction of the efferent arteriole of the glomerulus, is a sequel to the mechanism which initiates the hypertensive process. There is no evidence in their observations that renal

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123. Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Hypertension, *J. A. M. A.* **117**:92 (July 12) 1941.

124. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subject with Essential Hypertension, *J. Clin. Investigation* **20**:637 (Nov.) 1941.

ischemia can be regarded as the cause of essential hypertension. Certainly renal ischemia can initiate the mechanism of hypertension, but whether the secondary ischemia (as they regard it) associated with hypertonus of the efferent glomerular arteriole adds to the progress of the disease or is merely the result of some other initiating mechanism remains unanswered.

They are also of the opinion that as a result of the hypotonus of the efferent glomerular arteriole there is progressive impairment of tubular function which progresses at different rates in different persons. In some subjects this tubular impairment seems to exceed impairment of glomerular function.

Certainly there seems to be profound impairment of tubular function and ultimately destruction, which appears to be the essential characteristic of the kidney of hypertension, inasmuch as most observers using these methods are in agreement. The suggested possibility for error lies in the interpretations placed on the results obtained by these methods.

Chasis and Redish<sup>125</sup> found that the process of tubular impairment progresses at the same rate in both kidneys of patients with essential hypertension when impairment is measured according to blood flow. The disturbance in blood flow and filtration rate is exactly the same. They found no evidence of unilateral ischemia.

Wilkins and Duncan<sup>126</sup> studied the effects of angiotonin in normal human subjects by intravenous infusion. Arterial hypertension can thus be produced and controlled by regulating the rate of administration. This hypertension is accompanied by increase in cardiac size and decrease in cardiac output. There is a bradycardia, which the authors regard as vagal in origin. There are an increase in venous pressure, a decrease in vital capacity and an increase in circulation time. There were no significant electrocardiographic changes. There seemed to be some decrease in blood flow in the extremities. The patients experienced some nausea, headache, substernal oppression and palpitation.

All of the effects disappear within a few minutes when administration is stopped. If the substance is injected intradermally, local blanching of the skin is said to occur.

Abell and Page<sup>33</sup> have also studied the effects of angiotonin, renin and other pressor substances on the blood vessels and compared the effects. These observations were made in transparent chambers in rabbit's ears. The results may be summarized as follows: Both renin and

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125. Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, *J. Clin. Investigation* 20:655 (Nov.) 1941.

126. Wilkins, R. W., and Duncan, C. N.: The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, *J. Clin. Investigation* 20:721 (Nov.) 1941.

angiotonin in small doses cause constriction of the arterioles. The capillaries are not affected, and the venules show but little evidence of constriction. The blood flow is not reduced under ordinary dosage. Parahydroxyphenylethylamine and methylguanidine sulfate act in the same general way.

Equivalent amounts of epinephrine and pitressin result in extreme vasoconstriction of the arterioles. The constriction endures for a much longer time, and the peripheral blood flow is markedly reduced or abolished entirely. The venules also show a much more marked reaction, and the capillaries are not affected at all.

Thus by direct observation it is noted that angiotonin and renin react in the manner postulated to fulfil the requirements for the hypertensive mechanism. That is, they elevate blood pressure by moderate arteriolar constriction but have no effect in reducing blood flow. The force of the heart beat is also increased. Parahydroxyphenylethylamine and methylguanidine act in a similar manner, but epinephrine and pitressin produce such extreme arteriolar constriction that blood flow is impeded.

Landis<sup>127</sup> observed the effects of heat-treated extracts of the kidneys obtained at autopsy from 16 persons with normal blood pressure and 34 with well marked hypertension. Extracts from patients with benign hypertension and chronic glomerulonephritis used in the assay on anesthetized nephrectomized rabbits were without greater effect than those from patients with normal blood pressure. The extracts prepared from 4 patients with malignant hypertension all showed an augmented pressor activity but with a variation in activity which was so great that definite conclusions could not be drawn. Pressor substances were obtained from all kidneys studied.

The pressor mechanism responsible for experimental hypertension, and probably for the clinical type, consists in the production by the kidney of increased amounts of renin. In the circulating blood this is altered by the renin activator, which is produced in the liver.<sup>128</sup> Angiotonin, the actual pressor substance is thus produced. If the renin activator is not manufactured by the liver in adequate quantity as a result of hepatic damage or by hypatectomy, blood pressure at the higher levels is no longer maintained. Animals in which the liver has been damaged or removed respond to injected angiotonin as before but not to renin alone.

The question as to whether the vascular mechanism in hypertension is abnormally sensitive to normal amounts of pressor substance (angio-

127. Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys, *Am. J. M. Sc.* **202:14** (July) 1941.

128. Page, I. H.; McSwain, B.; Knapp, G. M., and Andrus, W. deW.: The Origin of Renin-Activator, *Am. J. Physiol.* **135:214** (Dec.) 1941.



tonin) has been answered in the negative, as far as experimental hypertension is concerned.<sup>129</sup> Dogs with hypertension are no more susceptible to angiotonin than are normal animals. Renin, however, does cause a greater response, and this seems to be the result of increased formation of angiotonin within the animal from the combination of renin and its activator, which is apparently present in increased quantity in the liver of experimental animals.

#### THE COUNTERPRESSOR MECHANISM

Wakerlin and Johnson<sup>130</sup> have continued their observations on the production of what was thought to be an antiserum for dog renin in the rabbit and for hog renin in the dog. This has been extended to different species. It was found that antirenin could not be produced in homologous animals; that is, antirenin to rabbit renin could not be produced in the rabbit, but only in another species. But the antisera produced could neutralize the pressor effect of renin from other species as well.

As the result of daily injections of hog renin, the blood pressures of hypertensive dogs fell strikingly. Heat-inactivated hog renin and active dog renin were without effect. The serums of the dogs treated with hog renin only neutralized the pressor effects of renin. Daily intramuscular injections given similarly to dogs with normal blood pressure seemed to prevent the development of hypertension when these animals were subsequently operated on. The authors do not attempt to explain these actions but suggest the development of an antihormone.

Certainly it is impossible to make any estimate of the significance of these observations.

Page and his co-workers<sup>131</sup> have continued their observations of blood pressure-reducing extracts obtained from kidneys. There can be no doubt as to the presence of these substances, but so far their identity is not known, and the use of the extracts which the authors have obtained still yields occasional shocklike reactions. It is also still not possible to secure uniform preparations of high potency. The report alluded to here refers to observations on 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with hypertension in the so-called benign phase.

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129. Page, I. H.: The Pressor Response of Normal and Hypertensive Dogs to Renin and Angiotonin, *Am. J. Physiol.* **134**:789 (Nov.) 1941.

130. Wakerlin, G. E., and Johnson, C. A.: Effect of Renin on Experimental Renal Hypertension in the Dog, *J. A. M. A.* **117**:416 (Aug. 9) 1941.

131. Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Kempf, G. F.; Gambill, W. D., and Taylor, R. D.: The Blood Pressure Reducing Property of Extracts of Kidneys in Hypertensive Patients and Animals, *Ann. Int. Med.* **14**:347 (Sept.) 1941.

Similar results in the reduction of blood pressure of rats made hypertensive have been reported by Jensen and his associates.<sup>132</sup> They were able by the use of renal extracts to reduce the blood pressure in their experimental animals significantly.

#### MEDICAL THERAPY OF HYPERTENSION

Except for the experimental use of kidney extracts and improvements in surgical management there have been no advances in the management of hypertension with the possible exception of the use of vitamin A. No evaluation of this method has as yet been made.

Govea Pena and Villaverde<sup>133</sup> have treated 65 patients. Massive doses of vitamin A were used, as much as 180,000 international units daily. Within a few days lowering of pressure amounting to 30-50 mm. of mercury was noted. The dose was then reduced 50 per cent and continued for longer periods. The authors report prompt relief of the clinical symptoms, such as headache and vertigo. There were 4 patients with hypertension of the malignant type in the group, and they did not show any improvement. The authors recommend the administration of vitamin A by mouth.

The use of thiocyanate drugs has apparently increased. Barker, Lindberg and Wald<sup>134</sup> have an additional communication on the subject. Their results are about as previously reported, with nearly 50 per cent of patients significantly benefited when the concentration of these drugs in the blood was maintained within the effective range of 8-12 mg. per hundred cubic centimeters. Improvement usually occurred in two to four weeks, but sometimes three months of therapy was required. They emphasize that doses must be individualized to meet the needs of each patient.

There were no deaths from toxic reactions,<sup>4</sup> and relatively few patients showed toxic reactions requiring discontinuance of the drug. There were no severe toxic manifestations as long as the blood level was kept below 20 mg. per hundred cubic centimeters. Mild toxic symptoms, fatigue, anemia and dry scaling skin were not uncommon after prolonged therapy.

It is interesting to note that the authors state that in no case in which there was failure of response to thiocyanate therapy did splanchnic

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132. Jensen, H., and others: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts, *J. Pharmacol. & Exper. Therap.* **73**:38 (Sept.) 1941.

133. Govea Pena, J., and Villaverde, M.: Tratamiento de la hipertension arterial permanente por dosis altas de vitamina A, *Rev. cubana de cardiol.* **2**:332 (Sept.-Dec.) 1940.

134. Barker, M. H.; Lindberg, H. A., and Wald, M. H.: Experiences with Thiocyanates, *J. A. M. A.* **117**:1591 (Nov. 8) 1941.

section result successfully, but in such cases thiocyanates administered after surgical intervention produced a satisfactory response. No explanation is offered.

Severe poisoning in experimental animals (40-65 mg. per hundred cubic centimeters of blood) did not result in parenchymal damage except to the liver and bone marrow. It is interesting that these results resembled those reported by Page and associates<sup>128</sup> in their studies on the origin of the renin activator. The renin activator is produced in the liver, and it has been found that when the liver was damaged by carbon tetrachloride and alcohol, the production of renin activator failed.

Most of the recent reports on the use of thiocyanates bear out in detail the views of Barker and associates in regard to toxicity, dangers and effectiveness. In fact, the results reveal an almost startling similarity in percentages of benefit. It would seem that this is the only medical treatment which shows any degree of specificity in results beyond what may be expected from sedative, symptomatic treatment.

Among the papers presented in the past year on the subject the one by Kurtz, Shapiro and Mills<sup>135</sup> is interesting and contains observations which follow closely the results of Barker and co-workers. The first-named authors believe that the dangers of the proper use of potassium thiocyanate when blood levels are controlled weekly are small, but they emphasize that both the patient and the physician must be willing to cooperate fully in the control of the blood levels. Treatment should not be offered to a patient who is unwilling to subject himself to this control. Organic heart disease and even rather marked degrees of renal impairment have not proved to be contraindications in the hands of these investigators.

It is to be noted in this respect that Barker, Lindberg and Wald found that 2 patients with angina pectoris suffered attacks of precordial pain when their blood pressures reached too low a level. Reduction in dose and a restoration of a higher level of blood pressure resulted in relief.

That the contrary is also true can be stated by one of us (G. W. S.) who has seen frequent episodes of precordial pain accompanying periods of elevation of blood pressure. When these higher ranges of pressure were controlled with thiocyanate therapy, the episodes of precordial pain become much less frequent. Apparently, then, there is an optimal level of blood pressure for those patients with hypertension who have extensive visceral, particularly coronary, arteriosclerosis.

Although emphasizing that thiocyanates are only an adjunct to the treatment of hypertension, Hines<sup>136</sup> states that better results than ever

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135. Kurtz, C. M.; Shapiro, H. H., and Mills, C. S.: The Results of Sulphocyanate Therapy in Hypertension, *Am. J. M. Sc.* **202**:378 (Sept.) 1941.

136. Hines, E. A.: The Treatment of Hypertensive Disease, *Proc. Staff Meet., Mayo Clin.* **17**:184 (March 25) 1942.

before are obtainable today by medical treatment with the controlled use of these drugs. He points out that there is a wide range of individual tolerance to these drugs and marked variation in the rate of elimination. This is in agreement with the observations of other authors, including Blaney, Geiger and Ernst,<sup>137</sup> who made a carefully controlled study of the clinical use of thiocyanates by alternating periods of drug administration with periods during which a placebo was administered. No other treatment was used, and patients continued their daily routine of work, diet and rest, without alteration. The results obtained under this program were similar to those already discussed. About one-half the patients so treated were benefited.

Caviness, Umphlet, Peasley, Bell and Satterfield<sup>138</sup> report similar results for a group of 120 patients.

## A CRITICAL REVIEW OF THE LITERATURE ON SURGICAL TREATMENT

BY DR. DE TAKÁTS AND DR. MARCUS

### VENOUS THROMBOSIS

A great deal of attention is focused on the early recognition of small, subclinical thrombi. In a significant article Bauer<sup>139</sup> reiterates his previously expressed belief that a floating, femoral thrombus originates in the deep veins of the lower part of the leg and that it can be diagnosed by visualization of the superficial and the deep veins after injection of 35 per cent diodrast. When an early limited area of venous occlusion is discovered, the choice of treatment is heparin, which is administered in intermittent doses of 100 mg. three times a day. Heparin was given until the pulse became normal, usually for three to five days. Of 21 patients treated with nothing else but heparin, all were out of bed in six to eight days after the onset of symptoms. No further extension or embolization took place. Of 32 patients treated with lumbar sympathetic block, heat and elevation, the thrombosis remained localized to the lower portion of the leg in only 25 per cent; a propagation of the thrombus into the femoral vein took place in 75 per cent. In 31 per cent thrombosis became bilateral; in 16 per cent pelvic thrombosis occurred, causing 1 death. Large or small pulmonary infarcts were seen. The average length of stay in bed was forty-three days.

This small but carefully observed series seems to give heparin the first choice in the treatment of ascending thrombosis. Welch and

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137. Blaney, L. F.; Geiger, A. J., and Ernst, R. G.: Potassium Thiocyanate in Treatment of Hypertension, *Yale J. Biol. & Med.* **13**:429 (March) 1941.

138. Caviness, V. S.; Umphlet, T. L.; Peasley, E. D.; Bell, T. A., and Satterfield, G. H.: Potassium Sulfocyanate in Treatment of Hypertension, *North Carolina M. J.* **2**:275 (June) 1942.

139. Bauer, G.: Venous Thrombosis, *Arch. Surg.* **43**:462 (Sept.) 1941.

Faxon,<sup>140</sup> who are equally emphatic in emphasizing the value of venograms, distinguish between the inflammatory type of thrombophlebitis and the stagnant, bland phlebothrombosis. In the former type sympathetic block rapidly reduces temperature and edema; in the latter type ligation proximal to the thrombosed segment is recommended because of the danger of pulmonary embolism. In acute superficial phlebitis division of the saphenous vein at the groin is advocated; in deep phlebitis division of the femoral vein is done in all patients above the age of 40, as above this age the danger of embolism is markedly increased. Division of the femoral vein, preferably below the profunda, is indicated at any age if an infarct has already occurred. When infarcts have occurred but the source of thrombosis is not evident, venography is done on both sides, and if thrombosis is detected, ligation of the femoral vein on the corresponding side is undertaken.

Equally active intervention is advocated by Starr, Frank and Fine.<sup>141</sup> They believe in doing venography on both sides as thrombosis of the deep veins is frequently bilateral, and ligation of one femoral vein may be followed by pulmonary embolism from the other side. Fine and Sears<sup>142</sup> advise routine ligation of the femoral vein when thrombosis of the deep veins of the lower portion of the leg is present or suspected. If the profunda and the saphenous vein are open, there is no permanent edema resulting from the ligation of the femoral vein. The authors feel that heparin is too expensive, its use requires a great deal of nursing care and its administration is a burden to elderly patients, who have to be kept immobilized with intravenous drip apparatus.

Enthusiasm for venography is somewhat dampened by a report of Homans<sup>143</sup> on thrombosis as a complication of injection of 50 per cent diodrast. We have observed this ourselves in 2 patients.

It is our impression that careful clinical observations may often reveal the site of thrombosis without venography; if a patient is young, and no infarct has occurred; elevation of the foot of the bed, active motion in bed and small doses of heparin injected intermittently can be tried; if an infarct has occurred, there can be no question about the advisability of a ligation proximal to the thrombus. It is obvious, however, that often a thrombus has already reached the iliofemoral vein by the time a surgeon sees a patient. He has, in that event, the choice of ligating the external or the common iliac vein or aspirating the clot through the

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140. Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* **117**:1502 (Nov. 1) 1941.

141. Starr, A.; Frank, H. A., and Fine, J.: The Venographic Diagnosis of Thrombophlebitis of the Lower Extremities, *J. A. M. A.* **118**:1192 (April 4) 1942.

142. Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein, *Ann. Surg.* **114**:801 (Oct.) 1941.

143. Homans, J.: Thrombosis as a Complication of Venography, *J. A. M. A.* **119**:136 (May 9) 1942.

femoral vein. The latter method seems far simpler for the patient. Intermittent administration of heparin makes its use less cumbersome and also less expensive than the continuous drip method.<sup>144</sup> The recently advocated dicoumarin 3,3'-methylenebis-4-hydroxycoumarin,<sup>145</sup> inexpensive and orally administered, is still not past the experimental stage. Its daily control by accurate determinations of prothrombin prohibits its use in the home or in the smaller hospital. Its damaging action on the liver is still not above suspicion.

#### ARTERIAL OCCLUSIONS

The management of acute embolic occlusions of peripheral arteries is discussed by Atlas.<sup>146</sup> He reports 2 cases in which minute emboli lodged in the periphery of the leg and gave rise to bilateral vasospasm of such magnitude that a saddle embolus of the aorta was simulated. In both cases the patients were treated conservatively, and within twenty-four and seventy-four hours, respectively, pulsations returned to the extremities.

The conservative measures employed were: intravenous administration of papaverine, administration of heparin, protection of the limb by an unlighted cradle and wrapping the limb in cotton. After the initial spasm disappears, collateral circulation may be stimulated by mild local heat, rhythmic venous occlusion or suction and pressure therapy. Embolectomy is indicated if conservative measures fail to improve the ischemia.

In 2 other cases resection of thrombosed segments due to periarteritis nodosa produced almost immediate release of the reflex spasm in the collateral bed.

The observations of Atlas on the occurrence of small emboli producing ischemia out of proportion to the extent of organic occlusion are of great clinical interest. Certainly many massive arterial occlusions are preceded by showers of just such emboli, and if they were promptly treated with antispasmodics and anticoagulants further emboli or superimposed thromboses might be avoided.

Individual cases of successful embolectomy, in which early diagnosis and postoperative heparinization were stressed, were reported by Ravdin

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144. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, *J. A. M. A.* **116**:2831 (June 28) 1941.

145. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3,3'-Methylenebis (4-hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Blood of Dogs and Humans, *Am. J. M. Sc.* **202**:563 (Oct.) 1941.

146. Atlas, L. N.: The Management of Acute Embolic Occlusion of the Arteries to the Extremities, *Surg., Gynec. & Obst.* **74**:236 (Feb.) 1942.

and Wood<sup>147</sup> and Bancroft and Glick.<sup>148</sup> Pratt<sup>149</sup> reviewed 26 cases of arterial embolism in 12 of which embolectomy was performed, with 5 survivals. He reports 1 remarkable case in detail in which clots were removed from both femoral arteries sixty hours after the onset of a saddle embolus. The left leg recovered, but the right leg had to be amputated.

#### VASCULAR INJURIES

Mason<sup>150</sup> writes a timely article on the management of vascular injuries. Great improvement has been brought about by the use of blood transfusions when severe hemorrhage is encountered. He classifies most vascular injuries into those which demand immediate treatment and those in which a brief period of delay is permissible. There is finally a third group of those which come under observation at a late period. Traumatic aneurysms should not be operated on before the twelfth day after occurrence; this short delay gives sufficient time for the development of collateral circulation; the injured vessel may heal, and infection is less apt to occur. Occasionally, spontaneous healing may take place. The question of ligation versus suture is discussed in regard to war surgery. The dangers following ligation of large arterial trunks are especially great in an exsanguinated patient. These may be gangrene, trophic disturbances and muscle paralysis. To offset the results of sudden vascular occlusion caused by the ligature, certain mechanical and physiologic measures are available. Of the mechanical means, alternate suction and pressure, intermittent venous hyperemia and use of the Matas compressor are discussed. Preferred to these mechanical devices are the physiologic methods, such as sympathectomy or procaine block of the sympathetic nerves, which give striking improvement of circulation. Of course, arterial suture is always preferable to ligation except when severe infection is present or when ligation can be safely performed without jeopardizing the viability of the distal parts. The postoperative use of heparin has increased the number of favorable results.

For arteriovenous aneurysms of longer standing, quadruple ligation with excision of the sac is recommended because it is easier to do and because there is sufficient collateral circulation. In the earlier cases transvenous arterial suture is the method of choice.

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147. Ravdin, I. S., and Wood, F. C.: The Successful Removal of a Saddle Embolus of the Aorta, Eleven Days After Acute Coronary Occlusion, *Ann. Surg.* **114**:834 (Nov.) 1941.

148. Bancroft, F. W., and Glick, A. H.: Arterial Embolectomy, *Ann. Surg.* **114**:1093 (Dec.) 1941.

149. Pratt, G. H.: The Surgical Treatment of Peripheral Embolism, *Am. J. Surg.* **50**:566 (June) 1942.

150. Mason, J. M.: Treatment of Vascular Injuries, *Ann. Surg.* **114**:191 (Aug.) 1941.

The principles laid down in this paper are clearly defined and should be widely distributed to all those who may come in contact with war injuries involving large vessels of the extremities. Vascular injuries occur much more frequently during war than during peacetime. Their proper management may result in the saving of limbs and lives. Fractures, more dramatic and more mechanical, often overshadow concomitant impairment of circulation.

#### ANEURYSMS

Twenty-four cases of aneurysm of the abdominal aorta encountered at the Philadelphia General Hospital in ten years are reported by Eliason and McNamee.<sup>151</sup> In only 10 cases of the series was the aneurysm syphilitic; in the rest it was arteriosclerotic. In none of the cases was trauma an etiologic factor. In only half of the cases was the condition diagnosed correctly. The dominant symptom was pain, but its radiation was rather inconstant. Roentgenograms were made in 16 cases, in 11 of which erosion of vertebrae was evident. A pulsating mass could be felt in slightly over one half of the cases (54.1 per cent). Of the 16 cases in which autopsy was done, in 10 the aneurysm was ruptured, retroperitoneally in 9 and into the jejunum in 1. Of the 8 cases in which necropsy was not done, there was clinical evidence of rupture in 2.

Exploratory laparotomy was done in 7 cases, in 5 of which reparative work was done. In 3 cases the aneurysm was wired; in 1 case the left common iliac artery was ligated for ten days, and in another an arteriovenous anastomosis was attempted between the iliac vessels. Unfortunately, nothing is said about the results in the 5 cases.

From Guy's Hospital in London, Brock<sup>152</sup> reports in detail a case of aneurysm of an innominate artery in which ligation was successful. The operation still remains formidable, but successes obtained amply justify further attempts of surgical therapy.

Transthoracic, transpleural ligation of the first portion of the left subclavian artery is recommended by Touroff<sup>153</sup> for aneurysms or other conditions requiring a proximal ligature. The approach is through the front after-division of the second and the third costal cartilage. After the pleura is entered and the lung permitted to collapse, the first portion of the subclavian or the innominate artery is easily indentified and tied.

There is no danger of injury to the thoracic duct, the brachial plexus or adjacent large vessels at the root of the neck; also removal of portions of the clavicle, the sternum or ribs becomes unnecessary. Surgeons

151. Eliason, E. L., and McNamee, H. G.: Abdominal Aneurysm: A Report of Twenty-Four Cases, *Am. J. Surg.* 56:590 (June) 1942.

152. Brock, R. C.: Aneurysm of the Innominate Artery: Report of Case Treated Surgically, *Guy's Hosp. Rep.* 90:180, 1940-1941.

153. Touroff, A. S. W.: Transthoracic Transpleural Ligation of the First Portion of the Left Subclavian Artery, *Surgery* 10:747 (Nov.) 1941.



who have had to struggle in the past with aneurysms of the subclavian artery in the neck will welcome this approach.

Richards and Learmonth<sup>154</sup> performed a lumbar sympathectomy on the right side in a 30 year old patient, after which the right femoral artery was occluded by digital pressure for five minutes three times a day. The right foot was 11 C. warmer than the left one six days after sympathectomy. With these precautionary measures, an aneurysm of the right popliteal artery was excised, necessitating the ligation of the right popliteal and the right superior, medial and middle genicular arteries. After operation the right foot remained warmer than the left one, and muscle pain or wasting did not develop. The pedal pulses disappeared.

In our experience the combination of preliminary sympathectomy with an excision of an aneurysmal sac, especially in the popliteal region, has been most gratifying. In elderly patients with arteriosclerotic aneurysm a sympathetic block with alcohol will occasionally suffice to bring on spontaneous clotting in the aneurysmal sac.

Wildegans<sup>155</sup> reports 55 cases of traumatic aneurysm. Lately arteriography was employed to map out the extent and pattern of collateral circulation. He reports 7 cases in detail, in which one ligation and three lateral and one circular suture were done. Even in the circular suture he obtained good permeability of the artery.

While such feats are undoubtedly possible, especially with the aid of heparin, ligation and resection with preliminary sympathectomy is undoubtedly the simplest method and the one that is best applicable to the surgery of war.

Gamm<sup>156</sup> reports a case of arteriovenous communication between the anterior tibial artery and vein, which followed the use of a Steinmann pin. The heart did not become enlarged, but pulse pressure and pulse rate were elevated. The oscillometric and temperature readings were higher on the affected side. Operation consisted of tying the vein and lateral suture of the artery. Heparin was given intravenously for forty-eight hours. The pulsation of the dorsalis pedis artery was preserved, which is truly an excellent result.

#### CAROTID SINUS SYNDROME

Ray and Stewart<sup>157</sup> present 4 cases of hypersensitive carotid sinus reflex of the vagal type, in which the carotid sinus nerve and the

154. Richards, R. B., and Learmonth, J. R.: Lumbar Sympathectomy in the Treatment of Popliteal Aneurysm, *Lancet* **1**:383 (March 28) 1942.

155. Wildegans, H.: Die Arteriographie bei traumatischen Aneurysmen, *Chirurg* **13**:6 (Jan.) 1941.

156. Gamm, K. E.: Arteriovenous Fistula, *J. A. M. A.* **119**:134 (May 9) 1942.

157. Ray, B. S., and Stewart, H. J.: Observations and Surgical Aspects of the Carotid Sinus Reflex in Man, *Surgery* **11**:910 (June) 1942.

carotid body were removed. The complaints were uniformly those of recurring syncope. In all 4 cases bradycardia and syncope occurred when the carotid sinus was compressed. Pulse rate, blood pressure and electrocardiographic changes were recorded during and after compression, with and without protection with atropine.

On exposure the carotid arteries showed signs of moderate to severe arteriosclerosis with visible atheromatous plaques in the walls. The patients' ages varied between 58 and 68. After the operation there was no return of spontaneous attacks of syncope, and no changes could be induced by pressure on the carotid sinuses. During operation ether did not abolish the reflex response induced by pressure on the carotid sinus. The authors emphasize that the degree of response is in direct proportion to the suddenness and the amount of pressure on the carotid sinus.

They also report a cerebral type of hyperactive carotid sinus reflex, in which cure followed the excision of tuberculous nodes in the neck.

It is well to note that atropine given orally in the vagal type produced tachycardia and the usual unpleasant symptoms but did not protect patients against syncope. The frequent occurrence of local changes in the arteries or adjacent soft tissues on the side from which the hyperactive reflex can be elicited suggests that the abnormal reflex does originate in the sinus. These results, supported also by some of our unpublished observations, suggest that the cerebral, central origin of these reflexes, postulated by some workers, is not substantiated at least for one group of cases.

#### VASOMOTOR APPARATUS IN PERIPHERAL VASCULAR DISEASE

Van Buskirk<sup>158</sup> studied the recurrent branches of the communicating rami and found that some of them join anterior spinal roots at higher levels than the foramen through which they enter the vertebral canal. Such unmyelinated fibers may ascend as much as six or more segments. Thus an anatomic explanation is afforded for failure to obtain complete sympathetic denervation of the arm by extirpation of the stellate ganglion and the upper two or three thoracic segments of the sympathetic trunk. Fibers originating below the third thoracic segment ascend in the vertebral canal and may join the peripheral nerves of the upper extremity through the intervertebral foramina of the first thoracic and the lower cervical segments. If this work, done on cats, may be applied to human beings, it could explain some of the incomplete denervations or recurrences in upper extremities.

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158. van Buskirk, C.: Nerves in the Vertebral Canal: Their Relation to the Sympathetic Innervation of the Upper Extremities, *Arch. Surg.* **43**:427 (Sept.) 1941.

Kuntz and Dillon<sup>159</sup> found that in experiments on cats and monkeys reflex vasoconstriction of the digits of the upper extremity could be demonstrated after removal of the second and the third thoracic segment of the sympathetic trunk. They concluded that the first thoracic nerve must contain preganglionic fibers going to the upper extremity. If these conditions are present in human beings, complete sympathetic denervation of the upper extremity cannot be accomplished by any surgical procedure which leaves the stellate ganglion with its gray communicating rami intact and which does not interrupt the preganglionic components of the first thoracic nerve.

Because of a technical error in 1 of his cases Atlas<sup>160</sup> was able to observe the effects of the isolated removal of the third dorsal ganglion, whereas, on the other side the white rami of the second ganglion were destroyed. On the side of the incomplete preganglionic section the sympathetic denervation of the arm was incomplete. This is contrary to the experience of Livingston, who stated that removal of the third ganglion results in adequate sympathectomy of the arm. Atlas stresses the importance of removing the third rib posteriorly and identifying the level of segments to be removed.

These three articles are cited to present the still unsolved problem of freeing the upper extremity from vasomotor control. In previous reviews we have cited the contention of White and Smithwick, again expressed in their admirable monograph,<sup>161</sup> that in the upper arm preganglionic section is preferable to the postganglionic one. They have never found any reflex sweating or vasomotor activity after operation and have stressed various methods to prevent regeneration of the cut segments. In addition to their work on patients, the work of Sheehan and Marrazzi<sup>162</sup> may be cited; the last-named authors failed to find any sympathetic fibers in the first thoracic segment of monkeys going to the upper extremity which could be detected by as sensitive a recording mechanism as the cathode ray oscillograph.

Clinically, it all revolves around the problem of resecting or leaving the first thoracic outflow intact. The test case is that of Raynaud's disease, in which most of the sensitizations, recurrences and regenerations

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159. Kuntz, A., and Dillon, J. B.: Preganglionic Components of the First Thoracic Nerve: Their Role in the Sympathetic Innervation of the Upper Extremity, *Arch. Surg.* **44**:772 (April) 1942.

160. Atlas, L. N.: The Role of the Second Thoracic Spinal Segment in the Preganglionic Innervation of the Human Hand—Surgical Implications, *Ann. Surg.* **114**:456 (Sept.) 1941.

161. White, J. C., and Smithwick, R. H.: *The Autonomic Nervous System: Anatomy, Physiology and Surgical Application*, ed. 2, New York, The Macmillan Company, 1941.

162. Sheehan, D., and Marrazzi, A. S.: Sympathetic Preganglionic Outflow to Limbs of Monkeys, *J. Neurophysiol.* **4**:68 (Jan.) 1941.

seem to occur. Personal observations on preganglionic and postganglionic sympathectomies performed on the two extremities of the same patients impress us at present with the superiority of preganglionic section.

Hyndman and Wolkin<sup>48</sup> submit considerable evidence that Raynaud's disease is primarily not a disorder of the sympathetic nervous system but, as contended by Lewis, is a local vascular fault. They attribute the beneficial effect of sympathectomy to the relief from pain due to exposure to cold. They also believe in the existence of afferent, pain-bearing sympathetic fibers, many of which course in the sheaths of major vessels. Their interesting line of thought, documented by careful clinical studies, is recommended for study to those working in this field. They feel that it is necessary only to remove the second thoracic ganglion in order to sympathectomize completely the upper extremity. The trauma incident to the removal of the stellate ganglion may be the reason for better results of the preganglionic section.

Atlas<sup>163</sup> describes a patient suffering from deep, constant, aching pain in an anesthetic area of hand and fingers which followed injury to the median nerve. He feels that the painful and trophic phenomena were caused by vasospasm due to sensitization of the peripheral vessels to epinephrine. The postganglionic fibers to these vessels were cut in the median nerve. A preganglionic sympathectomy gradually relieved the pain and cyanosis.

The interpretation of these results is not easy. Other mechanisms may be suggested for the explanation of the relief from pain. The problem arising here is the same encountered in Sudeck's atrophy, where sympathectomy relieves the pain presumably by washing out or neutralizing the pain substances arising from continuous efferent stimulation of posterior root fibers.

Richter and Woodruff<sup>164</sup> describe a simple and accurate method for mapping out areas which have been sympathectomized. These areas show a high electrical resistance to the passage of a small direct current. The areas of high resistance produced by sympathectomy closely follow the sensory dermatomes. The method can be applied to determine the success of an operation or the presence of regeneration.

We have used such a test several years ago and can fully confirm its accuracy and sensitivity. For practical purposes, however, the warm dry and cold damp areas in a sympathectomized limb can be readily detected by a palpating hand. Streaks of nondenervated segments cer-

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163. Atlas, L. N.: Further Observations on the Etiology of Vasomotor Disturbances Following Peripheral Nerve Section, *Surgery* 10:318 (Aug.) 1941.

164. Richter, C. P., and Woodruff, P. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, *Surgery* 10:957 (Dec.) 1941.

tainly follow sensory dermatomes. Their presence should be looked for after all sympathectomies.

Traumatic arterial spasm is of increasing importance during war. The use of violent traction methods may precipitate arterial spasm. Cohen<sup>165</sup> feels that complete reduction of fractures may often be postponed for a few days with greater safety. The effects of prolonged vasoconstriction and consecutive ischemia are so serious, especially in potentially or actually infected limbs, that every effort must be made to overcome arterial spasm. Early exploration seems to be the most reliable method to release vasospasm.

Henry<sup>166</sup> presents several cases of comminuted fractures in which peripheral vasospasm may inhibit normal healing. Because of impaired circulation under such circumstances infections are more apt to develop in spite of thorough débridement and therapy with sulfonamide compounds. Lumbar sympathectomy abolishes vascular spasm and creates favorable conditions for control of infection and repair. He advocates the routine use of lumbar sympathetic block in severe trauma to the lower extremities.

Adams-Ray<sup>167</sup> recommends injection of procaine into sympathetic ganglions after frostbite of the extremities. He believes that even after the action of cold has ceased, there remains persistent local ischemia due to vasospasm, which produces painful sensory disturbances. The residual pain may also be due to injury to the local nervous tissue. Protracted and intractable sensory disturbances responded promptly to block of the sympathetic ganglions.

Surgical treatment of the sympathetic nervous system in cases of arteriosclerosis and thromboangiitis obliterans is of no value, according to Pennoyer.<sup>168</sup> When the nutrition of the tissues is impaired, the accumulation of metabolites produces arteriolar and capillary paralysis. This is the explanation of the pallor on elevation and rubor on dependence so commonly observed in such disorders. This metabolite control of circulation eliminates vasomotor control. Patients showing a rise in cutaneous temperature after nerve block offer a favorable prognosis for nonsurgical therapy, as the arterial system is elastic enough to be capable of improvement.

In our experience, removal of the vasomotor tone from a vascular tree with impaired circulation frees it from many repeated stimuli of

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165. Cohen, S. M.: Traumatic Arterial Spasm, *Guy's Hosp. Rep.* **90**:201, 1940-1941.

166. Henry, J. P.: Traumatic Vasospasm and Its Relationship to Wounds of the Lower Extremity, *Am. J. Surg.* **56**:49 (April) 1942.

167. Adams-Ray, J.: Novocaine Block of the Stellate Ganglion: Therapeutic Aid in Sensory Disturbances Caused by Cold, *Acta chir. Scandinav.* **85**:1, 1941.

168. Pennoyer, G. P.: Peripheral Arterial Occlusion, *Am. J. Surg.* **53**:102 (July) 1941.

reflex or central origin and favors the action of conservative measures, which tend to accelerate the development of collateral circulation. This is true of certain types of Buerger's disease and also some forms of arteriosclerosis in which vasospastic claudication develops.<sup>40</sup> Atlas,<sup>169</sup> however, has reported 3 cases of gangrene following lumbar sympathectomy. In all 3 the surface temperature of the feet rose appreciably after the operation, but nevertheless, patchy areas of necrosis appeared between one and two weeks after the operation, necessitating finally amputation through the thigh in all 3 cases.

For many years we have treated certain arteriosclerotic occlusions by blocking sympathetic nerves with alcohol. Improvement and better response to conservative therapy have been occasionally striking. Patients with continuous and intractable pain at rest, however, are often on the verge of gangrene, and the lowering of blood pressure, slowing of circulation, or increase in the coagulability of the blood following operation may well be the straw that breaks the camel's back. The explanation of Atlas, that arteriovenous shunts divert too much blood from the terminal vascular bed and the diversion is not compensated by increased flow from the collateral circulation, is a possibility which deserves further investigation. This report is a valuable warning to those doing sympathectomies for arteriosclerotic occlusion to regard continuous intractable pain at rest an immediate forerunner for gangrene. In fact, we believe that such a symptom defies all efforts at alleviation and indicates amputation.

#### SURGICAL TREATMENT OF HYPERTENSION

Powers and Murray<sup>111</sup> present a case of juvenile hypertension following unilateral pyelonephritis. The affected kidney was removed together with the major part of the adrenal. The blood pressure fell postoperatively but not to a normal level. The result of the cold pressor test returned to normal.

We have been rather disappointed with the effects of nephrectomy on hypertension in unilateral renal disease. The fact that one kidney is hypoplastic, contracted or functionless does not necessarily mean that its removal is followed by cure of the hypertension. Should the blood pressure begin to rise again, the patient, with hypertension and only one kidney, is in a less favorable position than before nephrectomy. It is our present impression that a bilateral splanchnic section should precede any nephrectomy; the latter operation might be tried if the splanchnic section has failed.

169. Atlas, L. N.: Lumbar Sympathectomy in the Treatment of Selected Cases of Peripheral Arteriosclerotic Disease, *Am. Heart J.* **22**:75 (July) 1941; Lumbar Sympathectomy in the Treatment of Peripheral Arteriosclerotic Disease: II. Gangrene Following Operation in Improperly Selected Cases, *ibid.* **23**:493 (April) 1942.

From the Lahey Clinic Bartels, Poppen and Richards<sup>170</sup> report on a series of 54 patients operated on for hypertension. Of these, 14 were operated on before 1935 and were not carefully selected. The operation before 1935 consisted of supradiaphragmatic splanchnicectomy and ganglionectomy. Nine of the 14 died during an average of twenty months after operation of causes related to hypertension. Four patients are still alive, but their blood pressure is just as high as before the operation. Another series of 41 patients operated on since 1935 was selected with definite criteria. They were under 40 years of age; their retinal vessels showed moderate sclerosis, and their hypertension was moderate to severe, with some fluctuation. They were subjected to a two stage subdiaphragmatic or transdiaphragmatic resection of the greater and the lesser splanchnic nerve and to the removal of the twelfth thoracic, the first lumbar and the second lumbar ganglion. The adrenal glands were visualized, and a biopsy specimen was taken from each kidney. If a sufficient amount of omentum was available, the left kidney was decapsulated and a nephro-omentopexy was carried out. Two deaths occurred after operation. Thirty-four per cent of the patients had a satisfactory drop in blood pressure; 26 per cent had a slight drop, and 39 per cent had no change at all. The average follow-up period was twenty-three months. Symptomatic improvement occurred in 71 per cent of patients, in spite of the fact that in half of them the blood pressure had not been altered. The authors feel that this high degree of symptomatic improvement justifies the operation, even though in only one third of the patients has the blood pressure been satisfactorily reduced.

Woods and Peet<sup>171</sup> took as the basis of their comparison cases reported by Wagener and Keith, in which five to nine year mortality statistics were available, and compared them with the mortality statistics of their seven years of follow-up records. In general, a favorable prognosis following operation seems to depend on the degree of retinal arteriosclerosis. In the malignant phase the mortality was 99 per cent in the medical, and 33 per cent in the surgical, series after five years.

The hypertensive state was classified as early, moderate, marked and malignant (Keith-Wagener) in a series of 30 cases reported by de Takáts, Heyer and Keeton.<sup>172</sup> Of the various technical methods for

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170. Bartels, E. C.; Poppen, J. L., and Richards, R. L.: Surgical Treatment of Hypertension (Results in Fifty-Four Cases), *Lahey Clin. Bull.* **2**:197 (Jan.) 1942.

171. Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension: II. Comparison of Mortality Following Operation with That of Wagner-Keith Medically Treated Control Series; a Study of Seventy-Six Cases, Five to Seven Years After Operation, *J. A. M. A.* **117**:1508 (Nov. 1) 1941.

172. de Takáts, G.; Heyer, H. E., and Keeton, R. W.: The Surgical Approach to Hypertension, *J. A. M. A.* **118**:501 (Feb. 14) 1942.

splanchnic nerve section, the transdiaphragmatic approach, consisting of the removal of the major splanchnic nerve from the fifth dorsal root to its entrance into the celiac ganglion and the excision of the ganglionated sympathetic trunk from the ninth dorsal to below the second lumbar ganglion, has given by far the best results and the only real reductions of high blood pressure. When such an operation was undertaken in various stages of hypertension, the degree of structural involvement determined the results. The malignant phase in a series of 8 cases has shown itself refractory to surgical treatment. The selection of cases of the early phase of the disorder and the employment of the extended splanchnic section, as described by Smithwick, seemed to be the important factors in obtaining good results. Outside of the actual lowering of blood pressure, which in turn may result in the diminution of the size of the heart and in improved electrocardiograms, an improvement in renal function, a marked postural hypotension with decrease in venous pressure and a decrease in reflex nervous irritability due to adrenal denervation have been observed. The latter may well be responsible for the symptomatic improvement, such as loss of headaches, palpitation and nervousness. In a few cases muscular implants into the kidney have been undertaken. The ultimate value of this procedure is still under scrutiny. The value of biopsy of the kidneys in predicting the results to be expected has become more and more clear as longer periods of observation have become available.

Grimson<sup>173</sup> reviews his previous experimental work, which tended to show that more might be accomplished by total paravertebral sympathectomy than by splanchnic nerve section. The renal type of experimental hypertension remains uninfluenced by total sympathectomy, but neurogenic hypertension does respond, at least for a time. In human beings the operation was carried out in three stages, two thoracic and one abdominal. At each thoracic operation the stellate ganglion, the thoracic sympathetic ganglionated chain, the entire splanchnic nerve and its branches and the major part of the celiac ganglion of the side in question are removed. The third stage, which is not always done, consists of bilateral lumbar sympathectomy down to or including the fifth lumbar ganglion. Eleven patients were operated on, 8 of whom had only the thoracic procedures. One death occurred after the first, and one after the second stage. The response of the patients varied from transient fall in pressure, followed by a restoration to almost the pre-operative level, to relatively normal pressures over a period of fourteen months. The lowering of blood pressure occurring after this extensive sympathectomy must be due to a decrease of peripheral resistance, since cardiorenal functions remain unchanged.

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173. Grimson, K. S.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in the Treatment of Hypertension. *Ann. Surg.* **114**:753 (Oct.) 1941.



The author is careful in drawing any conclusions as to the lasting merit of this surgical procedure. It appears, however, to lower blood pressure more consistently than does splanchnic nerve section.

The correlation of the author's experimental studies with his carefully conducted clinical observations makes this one of the most valuable and sound contributions to the surgical treatment of hypertension. There is this to be said, however, before his surgical technic can be widely adopted, that the operation carries a definite mortality; it is more extensive and probably too severe for some patients, who would receive benefit from a less extensive procedure. Furthermore, by operating on patients with early stages of the disorder in the future less extensive operations may suffice, as shown by our own experience. Attention should also be called to the fact that renal and neurogenic hypertension may not be so readily differentiated in human beings. Possibly all renal pressor substances act through the vasomotor center.<sup>174</sup>

AMPUTATIONS

Schlossmann and Gerber<sup>175</sup> present a histologic study of 74 gangrenous extremities coming to amputation. The role of mural or intimal hemorrhage was emphasized as the most frequent factor precipitating acute thrombosis. A classification of arterial lesions which ultimately produced gangrene and necessitated amputation was given as follows:

Lesion	Percentage
Thrombosis secondary to hemorrhage.....	49
Thrombosis on a plaque.....	7
Massive hematoma of the wall.....	1
Arteriosclerosis .....	23
Occlusion by granulation tissue.....	20

A study of the atheroma, its capillarization and the state of its stroma showed that intimal hemorrhage was secondary to rhexis of the vascular channels traversing the necrotic atheroma. Intimal and medial capillarization in arteriosclerotic vessels were traced both to the lumen and to the vasa vasorum. No difference was found between vascular sclerosis in diabetic and that in nondiabetic persons.

The same conclusion regarding the lack of difference between diabetic and nondiabetic arteriosclerosis was reached by Lisa, Magiday and Hart.<sup>176</sup> Changes in the veins were different. Acute venous thrombosis of the larger radicals was encountered less frequently among

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174. Dock, W.; Shidler, F., and Moy, B.: The Vasomotor Center Essential in Maintaining Renal Hypertension, *Am. Heart J.* **23**:513 (April) 1942.  
175. Schlossmann, N. C., and Gerber, L.: Peripheral Arteriosclerosis, *Ann. Surg.* **115**:292 (Feb.) 1942.  
176. Lisa, J. R.; Magiday, M., and Hart, J. F.: Peripheral Arteriosclerosis in the Diabetic and Nondiabetic, *J. A. M. A.* **118**:1353 (April) 1942.

diabetic patients, and the same was true of phlebosclerosis. Lymphangitis was encountered in the presence of infection, whether diabetes was present or not; pathologic changes in the nerves could not be demonstrated in either group. Dry gangrene occurred with frequency in both groups.

Macey and Bickel<sup>177</sup> present a ten year review of 264 amputations of lower extremities in patients with occlusive arterial disease. The clinical diagnoses were thromboangiitis obliterans, arteriosclerosis obliterans with and without diabetes and acute arterial occlusion. In amputations through the thigh a long anterior and a short posterior flap was used. Alcohol or procaine hydrochloride was injected into the large nerves before they were severed. Below the knee a long posterior and a short anterior flap was used. The crest of the tibia was beveled and the fibula sectioned 1 to 2 inches (2.5 to 5 cm.) higher than the tibia. The wounds were all closed snugly except in the presence of lymphangitis or cellulitis. Gas gangrene was a potential complication in the presence of an open lesion with gangrene.

Twenty-five patients with thromboangiitis obliterans who were operated on below the knee had complications, with 22 reamputations; 3 patients had amputations through the thigh, with reamputation necessary in 1 case. One patient was operated on through the knee joint (Gritti-Stokes), and it was necessary to reamputate the leg above the knee. Of 63 patients without complications, amputation was through the lower part of the leg in 38, the thigh in 29 and the knee in 1.

Of 80 patients with arteriosclerosis obliterans without diabetes, postoperative complications developed in 22 and 13 died. Of the 13 who died, 12 had amputations through the thigh and 1 below the knee. The remaining 9 had difficulties with the stump healing, and 6 patients had to have reamputations.

Of 61 patients suffering from arteriosclerosis with diabetes, 18 had complications due to impaired circulation, sloughing or infection in the stump and 2 had gas gangrene. Seven of these 20 patients died.

Of the 16 patients with acute arterial occlusion, 4 died. These had associated diseases, 3 having rheumatic cardiac lesions. Fifteen amputations were done through the thigh, and 1 disarticulation was done through the hip joint. The popliteal artery was occluded in 10 patients, the femoral artery in 5 and the posterior tibial artery in 1. In 9 of the 16 patients the postoperative course was uneventful; in 2 patients healing was delayed. In another patient reamputation was required. Acute arterial occlusions seemed to be more frequent on the right side.

The number of reamputations and the poor results of amputations through the lower portion of the leg are the two striking features of this

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177. Macey, H. B., and Bickel, W. H.: Amputation of Lower Extremities in Occlusive Arterial Diseases: A Ten-Year Review, *Surg., Gynec. & Obst.* **74**:821 (April) 1942.

review. It is our belief that a close study of the level of circulatory insufficiency minimizes the necessity for reamputations. It is also our impression that flapless amputations of the lower portion of the leg show a much larger percentage of primary union than the method used by the authors. Also, amputations following acute arterial occlusions should not be delayed until demarcation occurs.

Amputation of gangrenous parts by a necrotizing chemical agent is described by Mohs, Sevringhaus and Schmidt.<sup>178</sup> This chemical escharotic stimulates the development of an exceptionally healthy, highly vascular and germ-resistant granulation tissue. The technic used is to surround the gangrenous part with this fixative, which consists of a 40 per cent concentration of zinc chloride in a plastic base and which is applied about 2 mm. thick for twenty-four hours. There is no pain or bleeding, and the patient may walk around during the healing. The necrotic tissue is always cut through fixed tissue. Of a series of 66 cases, complete separation and healing occurred in 60.6 per cent. Failure in 10 cases was due to incomplete separation of the basal layer. In 6 cases there was extension of the gangrene; in 4 cases the patients signed their releases before completion of treatment, and in 4 cases the patients died of intercurrent diseases before healing occurred. No deaths were attributed to this procedure, and no breakdown of the scar occurred once healing took place.

The criteria which seemed to offer a favorable response to this treatment were (1) diabetic gangrene, for which the prognosis is better than for senile arteriosclerosis; (2) young patients, for whom the outlook is better; (3) patients showing good demarcation, in whom the response is better; (4) evidence of good reaction from living tissue; (5) strong pulsation of pedal arteries, and (6) good histamine flares on the foot. A high degree of arteriosclerosis offered a poor prognosis.

If this method proves to be successful in other series of cases, much will have been accomplished for a large group of elderly arteriosclerotic patients, in whom gangrenous toes with intractable pain necessitate a major amputation. Most of these patients are too feeble and too poor to hope for rehabilitation. The method certainly deserves trial, and further reports will be awaited with interest.

6 North Michigan Boulevard.

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178. Mohs, F. E.; Sevringhaus, E. L., and Schmidt, E. R.: Conservative Amputation of Gangrenous Parts of Chemosurgery, *Ann. Surg.* **114**:274 (Aug.) 1941.

## News and Comment

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**American Association for the Advancement of Oral Diagnosis.**—The ninth annual congress of the American Association for the Advancement of Oral Diagnosis will be held in Boston November 12 and 13 at the Forsyth Dental Infirmary.

The subject of this year's congress will be "The Military Aspects of Oral Diagnosis."

Members of the medical and the dental profession in the United States and the countries of the Western Hemisphere who are interested are cordially invited to attend and may obtain programs by communicating with the secretary, H. Justin Ross, 515 Madison Avenue, New York.

**Federation Proceedings.**—The Federation of American Societies for Experimental Biology, composed of the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists, has begun (1942) the publication of the *Federation Proceedings*.

Four issues will be published annually. Each year the March issue will contain the complete federation program of the scientific sessions of all the component societies as prepared for the forthcoming annual meeting, with abstracts of all scientific papers to be presented; the June and September issues will contain the full text of twenty or more papers presented at the annual meeting, including probably the papers on the joint society program and papers of several society symposiums; the December issue will contain material pertinent to the federation membership, i. e., the names of the officers and the membership list, together with an index of the completed volume.

The subscription price is \$4 (\$4.75 foreign), payable in advance. Subscriptions should be sent to Dr. D. R. Hooker, Managing Editor, 19 West Chase Street, Baltimore, Md.

## Book Reviews

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**A Manual of Pharmacology and Its Applications to Therapeutics and Toxicity.** By Torald Sollmann, M.D. Sixth edition. Price, \$8.75. Pp. 1,298. Philadelphia: W. B. Saunders Company, 1942.

The sixth edition of this book on pharmacology is welcomed. The plan of this edition conforms to that of the fifth. The material is presented as before, so that the manual can be useful as a book for students and as a reference volume. The important general information of interest to students is presented in large type, while experimental details are printed in fine type. The author continues to increase the use of English terminology, although Latin terms are also given. This edition is larger than the preceding one. There is an extensive bibliography at the end of the book.

The reviewer considers it unfortunate that the author has not included a section on vaccines and serums. This certainly is an important aspect of pharmacology and therapeutics. The use of such agents is not only important during peacetime but is extremely important at present, when so many people from many sources are being congregated. Again, with a right increase in the emphasis on the prevention of disease in therapeutics, there is a need for greater emphasis on prophylaxis in textbooks on pharmacology. The section on the sulfanilamide compounds is well, but too briefly, presented. A more complete discussion is indicated when one realizes the extent to which these drugs are being employed by physicians throughout the world. The significance of these criticisms should not be overemphasized. The volume continues to be excellent and is recommended highly for a concise and crisp discussion of therapeutic agents.

**The Eye Manifestations of Internal Diseases.** By I. S. Tassman. Pp. 542, with 201 illustrations, including 19 in color. St. Louis: C. V. Mosby Company, 1942.

The reviewer was somewhat disappointed after seeing the title of this book to find many of the discussions of ocular manifestations of internal disease to be inadequate. He was unable to find in the index a reference to "vitamins" or to "riboflavin." Night blindness is dealt with in a line which says it may be due to lack of vitamin A. The discussion of progressive exophthalmos in relation to thyroid disease is not really adequate nor is the discussion of the ocular changes associated with renal disease. It is the reviewer's impression that this book is the work of an ophthalmologist who has made a good effort to deal with the ocular phases of internal disease but who could perhaps profit by collaboration with a well trained internist.

**The Biology of the Negro.** By Julian Herman Lewis. Price, \$5. Pp. 433, with 17 tables. Chicago: The University of Chicago Press, 1942.

In clinics dealing with many Negro patients physicians are prone to make dogmatic statements about differences in the way disease manifests itself in Negroes and in white persons. That most of these popular views are not founded on actual fact is immediately obvious when one looks through Lewis' extraordinarily thorough and well documented book on every aspect of the anatomy, the biology and the disease characteristics of the Negro. Almost any disease can be found in the index, and reference to the pages dealing with it invariably yields a complete and satisfactory discussion. This contribution, of the first order, will be invaluable to all physicians, especially those working in southern clinics.

**Dermatologic Therapy in General Practice.** By Marion Sulzberger and Jack Wolf. Price, \$5. Pp. 632, with 67 figures and 25 tables. Chicago: The Year Book Publishers, Inc., 1942.

This highly practical book by well known specialists in dermatology seems to fill the needs of a general practitioner in connection with cutaneous disease. There are many excellent illustrations and large numbers of prescriptions for lotions, salves, etc. Physical therapy and irradiation therapy are also adequately dealt with.

## ETIOLOGY OF ATYPICAL ("VIRUS") PNEUMONIAS WITH A BRIEF RÉSUMÉ OF RECENT DISCOVERIES

HOBART A. REIMANN, M.D.

W. PAUL HAVENS, M.D.

AND

ALISON H. PRICE, M.D.

PHILADELPHIA

During the past few years an increasing amount of attention has been given to a pneumonic syndrome which differs sharply from pneumococcic lobar pneumonia and from other familiar pneumonias of known causation. It has occurred in two general forms, one represented by a small proportion of cases of pneumonic involvement in epidemics of mild disease of the respiratory tract, like those cases described by Bowen,<sup>1</sup> Allen<sup>2</sup> and most other authors, and the other represented by isolated, sporadic, nonseasonal cases of severe disease, occurring chiefly in persons over 30 years of age. In the former the incubation period appears to be a matter of a few days, and in the latter it is longer, up to two weeks or more. Both forms are characterized by a gradual onset with dry inflammation of parts or all of the mucosa of the respiratory tract; chills or chilliness; slowly rising fever lasting one to three weeks and falling by lysis; delayed signs of migratory pneumonia, often bilateral; relative bradycardia; unproductive cough; headache; photophobia; sweating, and a normal leukocyte count. Therapy with sulfonamide compounds has no influence on the course of the disease; complications are rare, and the mortality rate is practically nil. Because of inability to associate any bacteria with the disease and because of epidemiologic, clinical and pathologic resemblances to certain pneumonias caused by filtrable viruses, a virus was surmised to be the cause,<sup>3</sup> and the term "virus" pneumonia came into common usage. Some persons prefer to

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From the Department of Medicine, Jefferson Medical College Hospital.

1. Bowen, A.: Acute Influenza Pneumonitis, *Am. J. Roentgenol.* **34**:168-174 (Aug.) 1935.

2. Allen, W. H.: Acute Pneumonitis, *Ann. Int. Med.* **10**:441-446 (Oct.) 1936.

(Footnotes continued on next page)

call the disease "atypical" pneumonia, which seems too vague, since any pneumonia not conforming to the typical lobar form is atypical. Such an ambiguous term as "typical atypical" pneumonia has already been employed. Many other clinically and anatomically descriptive names have been used, as is evident in the titles of the appended references, but until its apparent diverse origin is discovered, confusion in classification must be expected.

During an epidemic of mild disease of the respiratory tract in the winter of 1939-1940<sup>4</sup> a small number of cases of a severe form were encountered at the Jefferson Medical College Hospital, and the condition was tentatively regarded as "virus" pneumonia because of a similarity to the severe nonseasonal, sporadic disease observed the year before.<sup>3</sup> However, in 1941 and 1942 26 more cases of isolated, sporadic, non-seasonal disease occurred, which on epidemiologic grounds suggests that the etiologic agent of the epidemic form and that of the sporadic form may be different. In the last two years we have encountered 4 cases in October, 5 in December, 8 in January, 3 in February, 2 in March, 2 in April and 2 in May. The total number comprised about 15 per cent of all cases of primary pneumonias studied in the hospital in the same years.

Since "virus" pneumonia is rarely fatal in adults, only 2 necropsy reports on patients regarded as having the disease are available. In both instances<sup>5</sup> the histologic reaction in the lungs was composed chiefly of mononuclear cells, and no bacteria were present. This cellular response occurs in pneumonias caused by known filtrable viruses and, together with the presence of cytoplasmic inclusion bodies in the lungs of infants dying from a form of "virus" pneumonia,<sup>6</sup> supports the concept of virus causation. On the other hand, a similar histologic reaction is evoked by *Haemophilus pertussis*, *Pasteurella tularensis*, *Toxoplasma*, toxins and irritative chemicals, so that opinion cannot be based on pathologic changes alone.

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3. (a) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, *J. A. M. A.* **111**:2377-2384 (Dec. 24) 1938. (b) Reimann, H. A., and Stokes, J., Jr.: Epidemic Infection of the Respiratory Tract in 1938-1939: A Newly Recognized Entity, *Tr. A. Am. Physicians* **54**:123-127, 1939.

4. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, *Arch. Int. Med.* **65**:138-150 (Jan.) 1940.

5. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, *Bull. Johns Hopkins Hosp.* **67**:229-267 (Oct.) 1940. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X): A Report of Thirty-Two Cases with Two Deaths, *ibid.* **67**:268-305 (Oct.) 1940.

6. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, *J. Pediat.* **20**:405-420 (April) 1942.

Our only fatality in 1941-1942 occurred in a woman aged 49, who died on the twenty-second day of illness. Chronic pyelonephritis, acute focal hepatitis and bilateral pneumonia were encountered post mortem. Histologically, the alveolar exudate was uncharacteristic, consisting predominantly of polymorphonuclear cells, and an occasional alveolus was lined with a hyaline membrane. No bacteria were seen in stained sections from the pneumonic areas, and cultures from various areas were sterile.

#### ETIOLOGIC STUDIES

Since the first etiologic studies on the problem were made in 1938<sup>3</sup> a surprising array of diverse agents were found to cause the syndrome called "virus" pneumonia, but in most cases attempts to isolate a filtrable virus from blood, secretions and the lungs have failed. In the first trials a filtrable agent was recovered from 2 patients but was lost in animal passage before its etiologic relation could be tested.<sup>7</sup> Martin and Fairbrother<sup>8</sup> reported a similar experience. Weir and Horsfall<sup>9</sup> isolated a virus virulent for mongooses from patients with a disease ostensibly "virus" pneumonia. The virus was specifically neutralized by convalescent serum from infected animals and also by serum from the patients from whom the virus appeared to have come.

In 1938 Francis and Magill<sup>10</sup> reported the isolation of an unusual virus from patients with an influenza-like disease. The virus caused meningitis and pneumonia in inoculated animals and was named the virus of meningopneumonitis. Retrospective tests on some of the patients gave indirect evidence that they had been infected with the virus of influenza B. It is therefore uncertain whether the virus of meningopneumonitis came from the patients and was etiologically related to their disease or whether it was of animal origin. The authors pointed out the resemblance of the virus to the viruses of lymphogranuloma venereum, psittacosis, lymphocytic choriomeningitis and Theiler's encephalomyelitis of mice.

Eaton, Beck and Pearson<sup>11</sup> studied a localized outbreak of 6 cases of severe atypical pneumonia, 3 of them fatal. In 4 cases a virus was isolated which was similar to, yet not identical with, the virus of

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7. Stokes, J., Jr.; Kenney, A. S., and Shaw, D. R.: A New Filtrable Agent Associated with Respiratory Infections, *Tr. & Stud., Coll. Physicians, Philadelphia* 6:329-333 (Feb.) 1939.

8. Martin, A. E., and Fairbrother, R. W.: An Epidemic of Apparent Influenza, *Lancet* 2:1313-1315 (Dec. 23) 1939.

9. Weir, J. M., and Horsfall, F. L., Jr.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, *J. Exper. Med.* 72:595-610 (Nov.) 1940.

10. Francis, T., Jr., and Magill, T. P.: An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals, *J. Exper. Med.* 68: 147-160 (Aug.) 1938.



psittacosis. Curiously, this new psittacosis-like virus is also related to, or is identical with, the virus of meningopneumonitis, as shown by reciprocal complement fixation and active immunity tests in mice. A subsequent report by Rake, Eaton and Shaffer<sup>12</sup> added another unsuspectedly related virus to the group, namely, that of lymphogranuloma venereum. Each of these viruses—that of psittacosis, of a psittacosis-like infection, of meningopneumonitis and of lymphogranuloma venereum—causes meningitis, pneumonia and granulomatous infiltrations in the skin in experimental animals. The lesions in each infection are microscopically indistinguishable. Furthermore, serum from numerous patients with atypical pneumonia fixed the antigens of meningopneumonitis, psittacosis and lymphogranuloma venereum, and a cutaneous test with antigen of the last-named disease (the Frei test) gave positive results in 5 of 8 cases.<sup>12</sup> This evidence of striking immunologic relation of the four viruses, together with their morphologic and tinctorial resemblances, suggest that the viruses belong to a closely related group and may have originally arisen from a parent strain, probably residing in animals or birds, which subsequently has become diversified by passage and adaptive residence in different hosts and tissues.<sup>13</sup>

Of further interest in this respect is the occurrence of “fulmar” psittacosis apparently contracted from marine birds, as reported from Scandinavia,<sup>14</sup> of the isolation by Pinkerton and Swank<sup>15</sup> of another psittacosis-like virus from pigeons and the report of a case of probable psittacosis thought to have been contracted from pigeons.<sup>16</sup>

Meyer, Eddie and Yanamura<sup>17</sup> isolated the virus of a psittacosis-like disease from the lung of a patient who had been in contact with pigeons,

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11. Eaton, M. D.; Beck, M. D., and Pearson, H. E.: A Virus from Cases of Atypical Pneumonia: Relation to the Viruses of Meningopneumonitis and Psittacosis, *J. Exper. Med.* **73**:641-654 (May) 1941.

12. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, *Proc. Soc. Exper. Biol. & Med.* **48**:528-531 (Nov.) 1941.

13. Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationship of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, *J. Exper. Med.* **75**:21-33 (Jan.) 1942.

14. Rasmussen, R. K.: Ueber eine durch Sturmvögel übertragbare Lungenerkrankung auf den Faröern, *Zentralbl. f. Bakt. (Abt. 1)* **143**:89-93 (Dec. 30) 1938.

15. Pinkerton, H., and Swank, R. L.: Recovery of a Virus Morphologically Identical with Psittacosis from Thiamin-Deficient Pigeons, *Proc. Soc. Exper. Biol. & Med.* **45**:704-706 (Nov.) 1940.

16. Alicandri, H.: Psittacosis, *J. A. M. A.* **118**:1214 (April 4) 1942.

17. (a) Meyer, K. F.: Pigeons and Barn Yard Fowls as Possible Source of Human Psittacosis or Ornithosis, *Schweiz. med. Wchnschr.* **71**:1377-1379 (Nov. 1) 1941. (b) Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, *Proc. Soc. Exper. Biol. & Med.* **49**:609-615 (April) 1942.

many of which also proved to be infected with the same virus. Another patient apparently contracted the disease from infected chickens.<sup>18</sup> Meyer named the disease ornithosis to distinguish it from infection peculiar to psittacine birds.

Smadel and his associates<sup>19</sup> studied 2 unusual fatal cases of lymphocytic choriomeningitis, in both of which patchy pneumonic areas composed largely of mononuclear cells were present. In 1 case pneumonia was the sole lesion encountered post mortem. During the illness there was evidence of infection of the respiratory tract, but no clinical diagnoses could be made. The causative virus was isolated from the blood, the lungs and brain tissue.

Other recently discovered infections characterized by atypical pneumonia which clinically may resemble "virus" pneumonia are Q fever,<sup>20</sup> coccidioidomycosis<sup>21</sup> and toxoplasmosis,<sup>22</sup> yet the agents causing them are not viruses and seem unlikely to have been the cause of the widespread infection called "virus" pneumonia.

The possible relation of the psittacosis virus or the virus of a psittacosis-like infection (ornithosis) to the condition described as "virus" pneumonia is of great interest. It may be recalled that psittacosis was strongly considered in differential diagnosis in most of our cases<sup>3</sup> and also in the cases reported by other authors.<sup>23</sup> Complement fixation tests for psittacosis were<sup>24</sup> therefore made by Miss Margaret Wall, of the Hospital of the Rockefeller Institute, under the direction of Dr. Joseph E. Smadel, on serum from 8 recently ill patients and from several of those described in previous reports. The test gave a positive result in the following 4 instances.

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18. Meyer, K. F., and Eddie, B.: Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of a Human Infection, *Proc. Soc. Exper. Biol. & Med.* **49**:522-525 (April) 1942.

19. Smadel, J. E.; Green, R. H.; Paltauf, R. M., and Gonzales, T. A.: Lymphocytic Choriomeningitis: Two Human Fatalities Following an Unusual Febrile Illness, *Proc. Soc. Exper. Biol. & Med.* **49**:683-686 (April) 1942.

20. Dyer, R. E.; Topping, N. H., and Bengston, I. A.: An Institutional Outbreak of Pneumonitis: II. Isolation and Identification of Causative Agent, *Pub. Health Rep.* **55**:1945-1954 (Oct. 25) 1940.

21. Farness, O. J.: Coccidioidomycosis, *J. A. M. A.* **116**:1749-1752 (April 19) 1941.

22. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, *J. A. M. A.* **116**:807-814 (March 1) 1941.

23. Dochez, A. R., in discussion on Reimann and Stokes,<sup>3b</sup> pp. 127-128. Maxfield, J. R.: Atypical Pneumonia with Leukopenia, *Texas State J. Med.* **35**:340-346 (Sept.) 1939. Enders, J. F.: *Psittacosis: Virus and Rickettsial Disease*, Cambridge, Harvard University Press, 1940, pp. 529-554.

24. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, *J. Infect. Dis.* **65**:225-233 (Nov.-Dec.) 1939.

CASE 1.—F. C., aged 50, had a severe shaking chill which lasted about twenty-five minutes on Dec. 20, 1941. Her temperature was then 38 C. (100 F.) and the leukocyte count 10,000. She was given a course of sulfadiazine (2-[paraaminobenzene-sulfonamido]-pyrimidine) therapy by her own physician, without effect. Later the temperature varied between 39 and 40 C. (102 and 104 F.). There were dry, hacking, paroxysmal cough and profuse sweats requiring change of bed clothing. Chills recurred on three further occasions.

The patient came to the hospital on the fifteenth day of illness, with high fever, malaise and cough. She appeared to be moderately sick; the temperature was 39.5 C. (103 F.), the pulse rate 95 per minute and the respiratory rate 24 per minute. Besides an unusual redness of the oral mucous membrane, a few tender cervical lymph nodes and a small area in the right mammary region where a few seemingly unimportant rales were heard, there were no helpful diagnostic features. The leukocytes numbered 6,800; the sedimentation rate was rapid, 34 mm. in twenty-five minutes, and a blood culture was sterile. Tentative diagnoses of typhoid fever, tuberculosis and rheumatic fever were made. On the following day roentgen study showed a surprisingly large dense homogeneous shadow in the lower portion of the upper lobe of the right lung, suggesting lobar pneumonia. No abnormal physical signs were heard over this area, and without roentgen study the extensive involvement would have been overlooked.

The temperature persisted at a high level of 39.5 to 40 C. (103 to 104 F.) until the twenty-second day of illness, when each successive swing was lower, and finally it became normal on the twenty-ninth day. The pulse rate remained fairly constant at 100 per minute. The respiratory rate rose from 22 to 30 per minute on the twenty-second day. Profuse sweating occurred the following day. The highest leukocyte count was never over 10,000 and was without an unusual proportion of cells. Headache was severe during the second week, but there was only an occasional slight cough, without sputum, in spite of the striking shadows in the lung. Subsequent roentgenograms showed a further spread, then a melting, of the density in the upper lobe of the right lung, and on the twenty-third day the whole lower lobe became clouded, but never as densely as the upper lobe. The shadows disappeared four weeks after the onset of the disease. No abnormal physical signs except fine rales in the right mammary and axillary areas and at the base of the right lung posteriorly were ever heard.

A Frei test made on the seventh day of convalescence with lymphogranuloma venereum antigen prepared both from chick embryo and from mouse brain yielded negative results. The results of complement fixation tests for psittacosis were positive in the following dilutions: twenty-third day after the onset of illness, 1:8; thirty-fifth day, 1:32; eighth week, 1:256, and twelfth week, 1:128.

The results of the complement fixation test suggest that the patient was infected with the virus of psittacosis, of a psittacosis-like disease (ornithosis) or of meningo-pneumonitis.

CASE 2.—C. O., aged 45, went to bed with a "head cold" and malaise about Dec. 13, 1941. He failed to improve and on the third day began to cough and have chilly sensations. Headache was severe. Repeated examinations of the chest failed to reveal abnormal signs until the sixth day, when rales were heard in the lower lobe of the right lung. The patient was admitted to the hospital on the ninth day of illness, with the diagnosis of "virus" pneumonia. There were paroxysmal, unproductive cough and slight dulness and rales in the lower lobe of the right lung. The temperature was 40 C. (104 F.); the pulse rate averaged 90 per minute, and the respiratory rate was 25 per minute. There was no sputum to examine, and a smear

and a culture of the pharyngeal exudate revealed nothing of importance. The leukocytes numbered 8,000 per cubic millimeter.

There were several profuse sweats; the temperature after another peak at 40 C. (104 F.) declined gradually and reached normal on the fifteenth day of illness. Convalescence was uneventful. Serum taken on the twenty-fourth day of illness gave a positive complement fixation reaction for psittacosis in a dilution of 1:128. Serum taken nine weeks later gave a positive reaction in a dilution of 1:64. The result of the Frei test was negative.

CASE 3.—M. T., aged 59, "caught cold" about April 8; the condition was insignificant at first, but the temperature gradually rose to 40 C. (104 F.) after several days, accompanied by headache, chilly sensation, malaise, slight cough and pain in the right side of the chest. She was treated at home with sulfadiazine, without improvement. The cough became worse but unproductive. There were attacks of profuse perspiration. The patient was admitted to the hospital on the fourteenth day of illness. She was not in distress but was slightly cyanotic and dyspneic. The conjunctivas and the pharynx were injected. There were slight dulness and many fine rales in the right scapular and axillary regions. A roentgenogram showed a corresponding area of density, which later enlarged in size. The leukocytes numbered 8,000, 12,000, 7,000 and 11,000 on four occasions. The sedimentation rate was rapid, 30 mm. in forty-five minutes. The temperature of 40 C. (104 F.) on admission dropped gradually to 37.5 C. (99.5 F.) on the twenty-second day of illness, where it remained for another ten days before becoming normal. Clinical improvement occurred on the twenty-second day. Mice inoculated with a small amount of sputum survived more than six weeks.

Blood taken on the sixteenth and the thirty-fifth day of illness gave a positive complement fixation reaction for psittacosis in a titer of 1:64.

CASE 4.—L. M., a Negro aged 26, became sick on Jan. 10, 1941 with a chill followed by nonproductive cough, fever, pain in his chest and profuse sweating. His nose was obstructed; his eyes were red and painful, and there was slight pharyngitis. The symptoms became worse, with headache and dyspnea. A slight amount of sputum was raised. He entered the hospital on the fifth day of disease with a temperature of 40.3 C. (104.5 F.), a pulse rate of 110 per minute and a respiratory rate of 25 per minute. There were slight dyspnea, conjunctival injection, photophobia and a macular eruption on the face, the backs of the hands and arms and the body. The eruption disappeared in a day or two. The pharynx and the tonsils were inflamed, and the submaxillary and the anterior cervical lymph nodes were slightly enlarged and tender. The breath sounds in the base of the left lung and the apex of the right lung were harsh, and only a few rales were heard in the base of the left lung after cough. The abdomen was normal. A roentgenogram of the chest showed a great increase in the density of the hilar markings extending into the periphery of both lungs, with patchy areas of mottled density suggesting pneumonia superimposed on acute tracheobronchitis. Three leukocyte counts varied between 4,300 and 4,700. The sedimentation rate on two occasions was increased and reached 25 mm. in two hours. A blood culture was sterile, and the Wassermann reaction of the blood was negative. Repeated examination of the sputum showed only the usual flora to be present. Mice inoculated intraperitoneally with sputum all survived.

On the sixth day of illness rales were heard in scattered areas in both lungs. The temperature fell during the next few days and reached normal on the tenth day. Blood serum taken on the seventh and the twentieth day after the onset of disease and tested by Dr. Charles Armstrong gave strong protection against the

virus of lymphocytic choriomeningitis. Eleven months later neutralizing antibodies were still demonstrable by Dr. Smadel. Blood serum tested ten and twelve months after recovery also gave positive complement fixation for the virus of psittacosis in a dilution of 1:64.

Complement fixation tests for psittacosis were made on serum from the patients in cases 1, 3 and 9 of the 1938 series,<sup>3</sup> and from the patients in the case described in figure 6 and in 1 other case of the 1939 series.<sup>4</sup> All results were negative. The results are, of course, inconclusive because of the intervals of four and three years since the disease occurred.

#### COMMENT

In spite of the striking clinical similarities of a certain condition called "virus" pneumonia to psittacosis, even including in some instances mild neurologic symptoms, epistaxis and an exanthem; the sporadic nature of the disease, and the age group principally involved, it is impossible to classify it as psittacosis according to accepted criteria.<sup>25</sup> The chief differences are the evidence in some instances of "virus" pneumonia of person to person contagion, no contact with psittacine birds, the low mortality rate and the failure to isolate a virus.

In none of the 4 cases reported here, in which serum gave a positive complement fixation reaction for psittacosis, was there evidence of contact with known carriers of psittacosis or ornithosis, including pigeons, barnyard fowl or other pet birds, and contact with rats or mice was unlikely except in case 4. The patients could not recall exposure to persons sick with a disease of the respiratory tract prior to their own illness and did not transmit obvious infection to others. All mice routinely inoculated intraperitoneally with nasopharyngeal secretion to detect the presence of pneumococci lived more than fourteen days. Had the virus of psittacosis been present they would probably have died from the infection within this period, according to the test proposed by Rivers and Berry.<sup>26</sup>

The presence of complement-fixing antibodies for psittacosis in these cases is nevertheless of importance, particularly in cases 1 and 2, in which the titer rose and fell during early convalescence. The result in case 3 is less convincing, since the titer did not diminish during convalescence, and in case 4 the tests were made so long after the disease. The negative results of tests on the serum of patients who had pneumonia in 1938 and 1939 are of no significance because of the long time elapsed. Furthermore, the incidence of complement-fixing anti-

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25. Rivers, T. M.: Psittacosis, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, p. 66.

26. Rivers, T. M., and Berry, G. P.: A Laboratory Method for the Diagnosis of Psittacosis in Man, *Proc. Soc. Exper. Biol. & Med.* 29:942-944 (May) 1932.

bodies for psittacosis in the general population is unknown. Nevertheless, when positive results are obtained in 4 of 8 cases, they would seem to represent more than a fortuitous occurrence.

The positive results, as discussed previously, only suggest that one of the viruses of psittacosis, a psittacosis-like disease (ornithosis), meningopneumonitis and lymphogranuloma venereum may have been implicated, but in view of the evidence produced by other investigators and positive results in 4 of 8 cases it is likely that one of them was causally related to the disease in question. It is also apparent that these viruses are much more widely distributed in nature than heretofore believed.<sup>17a</sup> Instances of contact infection in our own studies and in those of other investigators suggest that human beings may also serve as reservoirs of infection.

The presence of strong neutralizing properties for the virus of lymphocytic choriomeningitis in the serum of the patient in case 4, in addition to complement-fixing bodies for the virus of psittacosis, is of interest in view of the recent report of Smadel and his associates<sup>19</sup> and the observation of Francis and Magill.<sup>10</sup> But here again, without actual isolation of the first-named virus it is not possible to claim causal relation of it to "virus" pneumonia on this basis alone because of the possibility of an anamnestic reaction and because specific neutralizing bodies are encountered in 10 per cent of normal persons.<sup>27</sup> Furthermore, the possible reciprocal relation between this virus and those of the psittacine group is not yet known.

From the studies mentioned and from the facts at hand the adoption of the term "virus" pneumonia is justified, but only to indicate a syndrome composed of a group of entities, each caused by a specific filterable virus, as for example, that of psittacosis and related infections, of influenza, of chickenpox,<sup>28</sup> smallpox or of lymphocytic choriomeningitis or perhaps the mungoose-infecting virus. Furthermore, certain agents other than viruses, like the Rickettsia of "Q" fever, the protozoan *Toxoplasma* and the fungus *Coccidioides immitis*, may also cause disease resembling the pneumonias caused by viruses. And lastly there is a large group of atypical pneumonias of which the cause is still unknown. Therefore, etiologic studies should be made in all cases of pneumonia, including the special serologic tests for lymphocytic choriomeningitis and for diseases caused by the psittacine group of viruses, and the disease named according to its etiologic agent whenever possible.

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27. Armstrong, C.: Studies on Choriomeningitis and Poliomyelitis, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1940-1941, vol. 36, pp. 39-65.

28. Waring, J. J.; Neuburger, K. T., and Geever, E. F.: Severe Forms of Chickenpox in Adults, with Autopsy Observations in Case with Associated Pneumonia and Encephalitis, *Arch. Int. Med.* **69**:384-408 (March) 1942.

## CONCLUSION

The term "virus" pneumonia is established to include a syndrome or a group of entities which may be clinically indistinguishable yet may be caused by a variety of known filtrable viruses. Clinically similar instances of pulmonary infection may be caused by known agents other than filtrable viruses, and numerous pneumonias occur in which the causative agent has not yet been determined. The latter at present had best be termed primary atypical pneumonia, etiology unknown.<sup>29</sup>

Indirect evidence of infection with psittacosis virus or the related viruses of a psittacosis-like disease (ornithosis), meningopneumonitis and lymphogranuloma venereum was obtained by complement fixation tests in 4 of 8 cases of a condition regarded as "virus" pneumonia. In 1 case the serum also gave strong protection against the virus of lymphocytic choriomeningitis. Any one of these viruses may be the cause of a form of virus pneumonia.

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29. Primary Atypical Pneumonia: Etiology Unknown, Official Statement, War Med. 2:330-333 (March) 1942.

# OBSERVED COURSE OF DIABETES MELLITUS AND INFERENCES CONCERNING ITS ORIGIN AND PROGRESS

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This report presents evidence in favor of the idea that the course of diabetes mellitus begins at birth, that inherent features predetermine the average rate of its progress, that its course is approximately half run before the disease is even recognized and that some years after recognition it may show progressive and permanent improvement. The data which permit these inferences may be obtained by a comparison of the amount of insulin required with the length of time the disorder has existed in comparable groups of diabetic subjects.

The course of diabetes mellitus is variable but is usually related to the age at which the disease appears. This fact is recognized by all clinicians who treat much diabetes. As expressed by Woodyatt,<sup>1</sup> "As a general rule . . . the greater the age at which diabetes appears the slower will be its subsequent course." Exceptions occur at all ages, but the usual course is rapid progress after it begins in early life and more benign behavior when it begins late.

Prior to the discovery of insulin this tendency was reflected in the early death of diabetic children. For example, before 1922, when insulin became generally available, 208 of Joslin's young patients in whom diabetes developed in childhood or adolescence lived only about two years on the average, whereas those patients in whom diabetes was recognized after the age of 40 lived at least four times as long.<sup>2</sup>

Another characteristic of the course of diabetes which is less generally recognized is its tendency to grow more severe the longer it exists, as a rule. Thus, in insulin-treated patients the amount of insulin required to maintain good control tends to increase roughly in proportion to the duration of the disorder. It may show temporary vari-

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From Northwestern University Medical School, Chicago, and Evanston Hospital.

1. Woodyatt, R. T.: Diabetes Mellitus, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1941, p. 687.

2. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 275.



ations in both directions due to modifying influences, such as painstaking or careless treatment or infection and other complications. But as the diabetes persists, more insulin is usually required, until a level is reached which is characteristic of the individual case, commonly 40 to 60 units daily with diets of moderate value.

In clinical practice the severity of diabetes mellitus may be judged by a variety of gages. Some of the more obvious are as follows: (1) the amount of food tolerated without excessive glycosuria and hyperglycemia (this is of value only in cases of mild diabetes); (2) the rapidity with which glycosuria and hyperglycemia develop and their magnitude under conditions creating them, such as excesses of food, deficiencies in insulin effect and infections; (3) the ease with which ketogenic acidosis occurs and its intensity; (4) the degree of sensitivity to excesses of insulin, and (5) the size of the daily insulin dose required to maintain good control.

From the standpoint of quantitative study it is obvious that the most useful of these gages of severity is the size of the dose of insulin. If subjects with typical diabetes of every grade could be watched for years under unchanged conditions of treatment, much could be learned. But diets and technics of insulin control change; so data obtained in such a manner would not be comparable.

Data of almost equal value may be obtained in another manner. Instead of comparing the amount of insulin needed by the same patients at different times, the insulin required by different patients may be compared at the same time. Such data, although lacking the advantage of measuring the progress of a given set of patients, do possess the advantage of being strictly comparable as to details of diet and insulin management, which seems equally important, if not more so.

Hence, a group of patients treated under uniform conditions was analyzed to determine the relation between the need for insulin and the duration of the existing diabetes at various ages. Interpretations of such data must be based on the assumption that in any group of patients managed by diets of uniform value the need for insulin gives a fair estimate of the severity of the diabetes and that an increased need indicates progression of the diabetes. It is clearly recognized that this assumption may be misleading in any individual subject. Variability in insulin sensitivity,<sup>3</sup> complications, exercise,<sup>4</sup> consistency of

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3. Radoslav, C. S.: Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, *Wien. Arch. f. inn. Med.* 8:395-412 (July) 1924. Himsworth, H. P.: Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, *Lancet* 1:127-130 (Jan. 18) 1936. MacBryde, C. M.: Response to Insulin as an Index to the Dietary Management of Diabetes, *J. Clin. Investigation* 15:577-589 (Sept.) 1936. Klatskin, G.: The Response of Diabetics to a Standard Test

treatment, emotion,<sup>5</sup>—these and other factors affect the need for insulin profoundly in individual subjects. Yet when groups of subjects are employed such irregularities are minimized by averaging, and errors from this source are probably fairly constant in all groups.

On the assumption that such data provide an approximate view of the course of diabetes mellitus it is possible to confirm and augment the idea that diabetes progresses more rapidly the earlier in life it begins and that up to a certain limit it becomes more severe the longer it exists.

Of greater interest, however, such data support the theory of the inherent nature of diabetes. They also provide a rough concept of the stage of "potential diabetes" preceding the recognizable onset of the disease, as well as the level of normal insulinogenic function which exists even before the potential stage is reached. Finally, these data suggest the possibility that diabetes may be a self-limited or curable disease after it exists for a long time.

#### METHOD

Each patient in a group of 166 with proved diabetes was judged carefully from three standpoints: first, the age at which the diabetes was recognized (age at onset); second, the length of time it was known to have existed up to the time of study (duration), and third, the daily dose of insulin necessary for satisfactory control of the diabetes (insulin dose).

These patients when studied ranged from 6 to 82 years of age. Their diabetes had begun at 2 years of age in the youngest and 77 years in the oldest. The age distribution was approximately uniform; about one quarter were less than 20 years old and one third more than 50 years old at the onset of diabetes. About two thirds were females.

In no case was any acute complication present at the time of study. Some chronic complications existed, particularly in the older patients; these subjects were not excluded, and the significance of their complications will be discussed later.

*Age at Onset and Duration of Diabetes.*—The age at onset was estimated in each case from a careful history of the date of onset of unmistakable symptoms or, if a patient was asymptomatic, of the first discovery of glycosuria. In practically all cases this date could be ascertained quite definitely with no probable error greater than a few months in the majority. In each case the duration of the diabetes up to the time of study was then taken for computation of group averages.

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Dose of Insulin, *ibid.* **17**:745-750 (Nov.) 1938. Burgert, P.; Scott, R., and Nadler, W. H.: A Comparison of Tests for Insulin Sensitivity, *Proc. Central Soc. Clin. Research*, 1938, p. 23.

4. Lawrence, R. D.: The Effect of Exercise on Insulin Action in Diabetes, *Brit. M. J.* **1**:648-650 (April 10) 1926. Gerl, A., and Hofmann, A.: Muskelarbeit und Insulinbedarf beim Diabetes, *Klin. Wchnschr.* **7**:59-63 (Jan. 8) 1928. Richardson, R.: Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, *J. Clin. Investigation* **13**:699 (July) 1934. Marble, A., and Smith, R. M.: Exercise in Diabetes Mellitus, *Arch. Int. Med.* **58**:577-588 (Oct.) 1936.

5. Woodyatt, R. T.: Psychic and Emotional Factors in General Diagnosis and Treatment, *J. A. M. A.* **89**:1013-1014 (Sept. 24) 1927.

Groups of subjects for averages were formed as follows: All patients were classified in seven groups of 12 to 39 each according to the decade of life in which diabetes began. Those in each decade were then further subdivided into six smaller groups of 1 to 8 patients (usually 4 or 5) according to the length of time the diabetes had existed. For example, there were 33 patients whose age at onset was 41 to 50 years, inclusive. These 33 patients were further subdivided into six subgroups, in which the average duration of diabetes was approximately one, two, five, eight, thirteen and twenty-three years, respectively, at the time of study.

In each of the subgroups the average daily dose of insulin required for good control (as defined in the following section) was taken as the insulin dose for the group.

*Insulin Dose.*—In all cases the diabetes was regulated according to uniform criteria for satisfactory control. These criteria were as follows:

1. The use of diets capable of maintaining or obtaining ideal weight at normal activity and sufficient for normal growth in children.

2. Carbohydrate to fat ratio in grams of about 1:1. Accordingly, the average adult diet contained about 2 Gm. of carbohydrate per kilogram of body weight, 1 Gm. of protein and 2 Gm. of fat, providing about 30 calories per kilogram. In diets for obese subjects the fat was arbitrarily reduced to permit weight reduction, the carbohydrate value remaining comparable to that of the diets for other patients.

3. Freedom from glycosuria and excessive hyperglycemia except in a group of patients susceptible to hypoglycemic symptoms. In those patients, as much insulin was used as possible without hypoglycemia and as little glycosuria as possible was permitted.

4. Freedom from frequent hypoglycemia.

5. Insulin effects predominantly from protamine zinc insulin in a single dose daily, often alone, but frequently supplemented by a small daily (rarely twice daily) dose of ordinary insulin.

These criteria conform to those in general use today in practice, their chief distinguishing characteristics represented by the use of diets of only moderate carbohydrate content, perhaps a little less liberal than average in this country but generous enough not to approach a ketogenic level. Their ketogenic ratio (FA/G, Woodyatt<sup>6</sup>) was about 0.8.

Preliminary adjustment was accomplished in the Evanston Hospital under quantitative conditions. Further minor adjustments were then made until the weight behavior became satisfactory and the amount of insulin required daily for good control became relatively stable. This daily insulin dose was then averaged with those of other patients with diabetes beginning in the same decade of life and existing for approximately the same length of time, in small groups of subjects as just described.

Some 20 per cent of the patients did not require insulin for control and were included in the group averages with insulin doses of zero. It would obviously be unfair for the purposes of this paper to omit them.

## RESULTS

The table shows the values obtained in this manner in each of about forty small groups of comparable subjects. The table also shows the number of patients responsible for the average values in each group.

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6. Woodyatt, R. T.: Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med. 28:125-141 (Aug.) 1921.

The chart shows graphically the insulin needed after various periods of diabetes in each decade. Each point on a curve represents the average for one of the smaller groups of comparable patients, with

*Daily Insulin Dose Required for Control of Diabetes in Various Age Groups at Various Stages of Its Course in One Hundred and Sixty-Six Subjects*

Age at Onset, Yr.		Number of Years Since Onset of Diabetes *							No. of Sub- jects	Average Annual Insulin Increment, Units †
Range	Average	0-1	1-3	3-5	5-10	10-15	15-30			
First Decade										
2-10	6	Insulin dose, units..	27	42	45	56	63	52	21	7.2
		Years since onset....	1—	2+	4	8—	13—	17		
		No. of subjects.....	3	4	2	4	7	1		
Second Decade										
11-20	14	Insulin dose, units..	20	44	52	74	56	40	18	5.1
		Years since onset....	1—	2+	4	8	13	22		
		No. of subjects.....	4	4	1	3	3	3		
Third Decade										
21-30	26	Insulin dose, units..	12	37	30	49	60	27	17	3.8
		Years since onset....	1	2+	4+	10	14	18		
		No. of subjects.....	1	4	4	1	2	5		
Fourth Decade										
31-40	37	Insulin dose, units..	15	12	50	29	40	16	12	3.2
		Years since onset....	1—	2	4	7+	14	19		
		No. of subjects.....	2	1	1	6	1	1		
Fifth Decade										
41-50	46	Insulin dose, units..	17	6	15	33	15	20	33	1.9
		Years since onset....	1—	2	5	8+	13	23		
		No. of subjects.....	5	4	2	16	4	2		
Sixth Decade										
51-60	55	Insulin dose, units..	5	18	9	12	31	26	39	2.0
		Years since onset....	1—	3—	4+	7	12+	20		
		No. of subjects.....	5	8	5	8	8	5		
Seventh and Eighth Decades										
61-77	66	Insulin dose, units..	24	12	18	21	23	..	26	4.2
		Years since onset....	1—	3—	4+	8—	13			
		No. of subjects.....	5	5	4	5	7	0		

\* In each of the small groups the insulin dose and the number of years since onset represent averages for those subjects in the group.

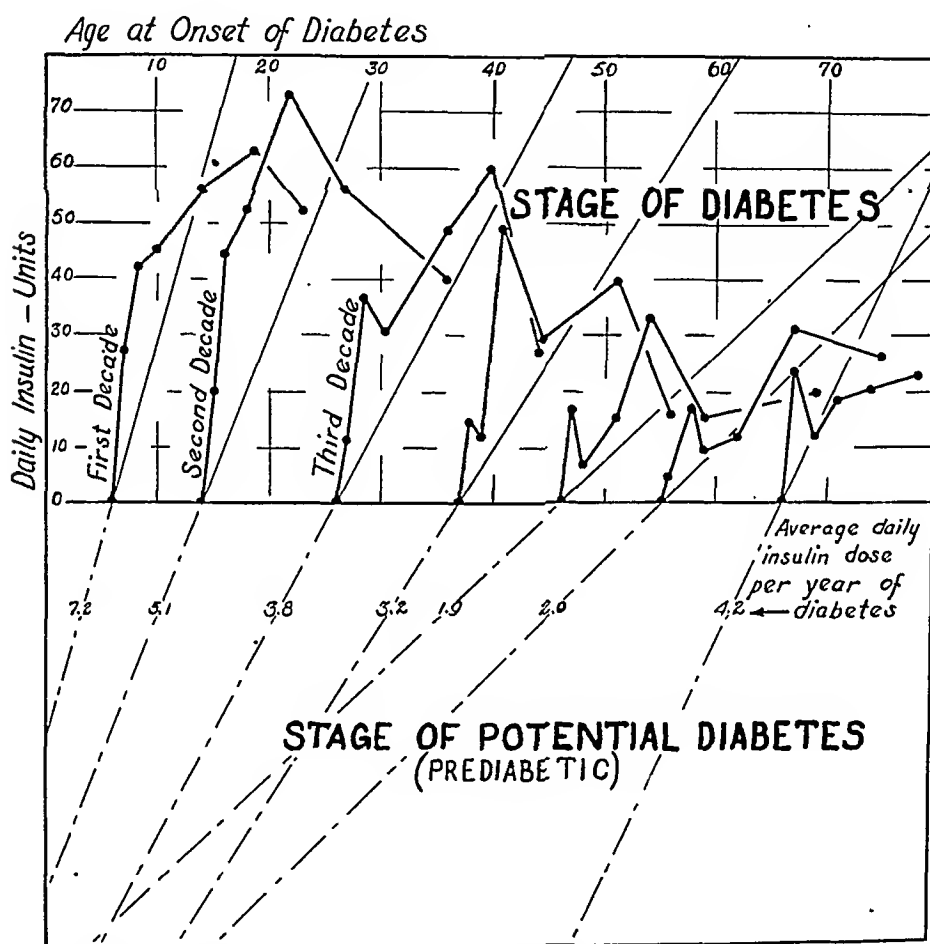
† The annual insulin increment in each decade was obtained by calculating the average rate of increase in required insulin in units per year of diabetes.

the insulin dose in units per day as the abscissa and the years of existing diabetes as the ordinate. The mean curve for each decade was obtained by calculating the rate of increasing need for insulin, or average annual increment, in units per year of diabetes. These increment curves were projected into the "prediabetic," or "potential diabetic," stage, on the theory that the rate of progression of diabetes is probably about the same before as after it makes its appearance clinically.

## INTERPRETATION

Four phenomena are apparent from a study of the actual insulin curves.

1. The earlier in life the diabetes appeared the more rapidly the need for insulin increased. This is true in all decades except the last, in which it is probable that the frequency of chronic complications increased the insulin required.



Relation between the age at which diabetes begins and the subsequent daily need for insulin.

2. Except for minor irregularities (discussed later) the longer the diabetes existed the greater was the need for insulin at all ages.

3. In all but the first two decades the initial rapid increase in insulin was followed by a temporary decrease, which occurred as early as the second or the third year and sometimes persisted through the fifth year of the disease. It tended to appear later and persist longer the greater the age at onset. Hence, it was probably missed in the first two decades because the data were not analyzed for periods shorter than the first year.

Individual examples of this phenomenon are well known, and it is usually anticipated in practice. Often there is complete freedom from the need for insulin for a short time following discovery and initial control of the diabetes. The improvement is probably due to a temporary gain in natural insulinogenic function due to accurate control. It does not appear to modify the ultimate course of the diabetes.

4. In all decades but the last there was an unmistakable tendency for required insulin to fall off somewhat after long persistence of the disease. Thus, after nine to fourteen years of diabetes (about ten on the average) in every decade up to 60 less insulin was required than previously. In a few individual subjects some thirty years of diabetes failed to alter this tendency toward improvement.

Two striking examples of this phenomenon are included in the group of 166 subjects. In 1 patient typical juvenile diabetes appeared at the age of 15. For fifteen years it followed the usual pattern of dependence on insulin in a dose as great as 50 units daily, difficulty of keeping under control, occasional severe acidosis or hypoglycemia and frequent glycosuria. Then at the age of 30 the insulin requirement began to decline. Five years later for about a year prior to death from chronic nephritis (intercapillary glomerulosclerosis<sup>7</sup>) insignificant glycosuria and hyperglycemia appeared when insulin was stopped, and doses as small as 10 units of protamine insulin caused hypoglycemia.

In another patient diabetes began at the age of 47. After about ten years of control by diet insulin was used continuously for about fifteen years in doses as large as 60 units daily. Heavy glycosuria occurred at intervals; there was no acidosis, and good health was maintained. Now, twenty-six years after the onset of the diabetes, this patient is exceptionally well at the age of 73, eats a generous diet only moderately restricted and for nearly a year has been free of sugar without any insulin whatsoever.

Cases in which diabetes disappears are described in the literature.<sup>8</sup> Every clinician who treats much diabetes observes an occasional instance.<sup>1</sup> It is not uncommon in the diabetes accompanying acromegaly.<sup>9</sup> However, a consistent tendency for ordinary diabetes mellitus to improve in time has not been noted previously.

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7. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, *Am. J. Path.* **12**:83-98 (Jan.) 1936. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulosclerosis: A Syndrome of Diabetes, Hypertension and Albuminuria, *Arch. Int. Med.* **64**:1252-1264 (Dec.) 1939. Porter, W. B., and Walker, H.: The Clinical Syndrome Associated with Intercapillary Glomerulosclerosis, *J. A. M. A.* **116**:459-464 (Feb. 8) 1941.

8. Naunyn, B.: *Der Diabetes mellitus*, ed. 2, Vienna, A. Hölder, 1906.

9. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, *Medicine* **6**:1-39 (Feb.) 1927.

The longer life span of a diabetic patient due to insulin makes it possible to observe the late course of the disease, especially in the case of patients who are young when diabetes begins. The tendency for required insulin to decrease eventually suggests the possibility of ultimate spontaneous cure of diabetes, assuming that patients can live long enough for it to occur. During the next ten or twenty years sufficient experience will have been gained to determine whether this course is usual or exceptional. The data here reported suggest that it may be the usual course after ten years or more.

The mean slopes are constructed by calculating the rate at which required insulin increases annually in each decade, i. e., the average insulin increment per year of diabetes. The minor decreases observed early and late are included in the averages as minus values, or decrements. Thus, on the average, the insulin required drops steadily from 7 units per year in patients with diabetes having its onset in the first decade to 2 units per year in patients with diabetes beginning in the fifth and the sixth decade.

If these average insulin rates are taken as approximate gages of diabetic progress in all decades, it is apparent from extension of their slopes that the origin and the magnitude of the prediabetic stage may be estimated. If one accepts the view that diabetes progresses at about these rates, both before and after it is recognized, two other important inferences involving the preclinical stage of diabetes are possible.

1. Its course begins about the time of birth, no matter how late in life it is recognized. In each decade except the last (in which chronic complications apparently alter the data), the average insulin curves showing the probable rate of progress tend to converge when extended backward into the "prediabetic stage." The point of convergence approximates the time of birth, indicating that diabetes of a predetermined type is inherited, begins its course at birth and progresses through an unrecognized phase at a rate which continues, with minor variations, after its discovery. This concept agrees with that which is generally accepted on the basis of other data.<sup>10</sup>

2. Its course is approximately half run by the time it is recognized clinically. The slopes which represent the average increments of insulin required annually tend to converge at an insulin level distant from that existing when the diabetes appears. If one grants that these average insulin curves represent the approximate course of the diabetes and that the course is about the same before as after discovery, the prediabetic stage appears to be at least as great in magnitude as the observed diabetic stage which follows. In other words, at least

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10. White, P.: Diabetes in Children, *Bull. New York Acad. Med.* **10**:347-357 (June) 1934; Recent Progress in Severe Diabetes, *Canad. M. A. J.* **35**:153-161 (Aug.) 1936. White, P., and Pincus, G., in Joslin.<sup>2</sup>

as much insulinogenic function is lost by a diabetic person before as after diabetes makes its clinical appearance.

This concept agrees with other data which indicate the magnitude of the normal capacity for utilizing sugar. Woodyatt, Sansum, Wilder and Felsher<sup>11</sup> found that nearly 1 Gm. of dextrose per kilogram per hour could be injected continuously into the veins of normal human beings and animals without glycosuria. In an average person weighing 70 Kg. during fourteen or fifteen hours daily of food absorption this would indicate a normal tolerance for dextrose of about 800 Gm. daily, which is about twice the amount of sugar tolerated by patients with the mildest known diabetes without glycosuria.

#### SUMMARY

If one employs the amount of insulin required daily for uniform control as a gage of the severity of diabetes mellitus in groups of patients of different ages and at different stages of the disease, the following interpretations appear to be justified:

1. Diabetes is inherent and begins at birth.
2. Before it is recognized in clinical practice it progresses through a stage the magnitude of which is fully as great as that of the known diabetes which follows recognition.
3. The rate of its progress is indicated by the age at which it is recognized. The earlier it appears, the more rapidly it progresses. It is probably more nearly correct to say the more rapidly it progresses through its unrecognized stage the earlier in life it appears.
4. During the first few years after its recognition it tends to improve temporarily, probably as a result of treatment. This improvement does not affect its subsequent course.
5. After some ten years of known existence there are indications that it may show progressive and permanent improvement.
6. These rules frequently appear to be violated in aged persons with diabetes, probably because of chronic complications.

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11. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, *J. A. M. A.* **65**:2067-2070 (Dec. 11) 1915. Sansum, W. D., and Woodyatt, R. T.: Studies on the Theory of Diabetes: VIII. Timed Intravenous Injections of Glucose at Lower Rates, *J. Biol. Chem.* **30**:155-173 (May) 1917. Felsher, H. V., and Woodyatt, R. T.: Studies on the Theory of Diabetes: IX. Sugar Excretion Curves in Dogs Under Intravenous Injection of Glucose at Lower Rates, *ibid.* **60**:737-747 (July) 1924.



# CINCHOPHEN GASTRIC ULCERS IN CHICKS

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The existence of a dietary factor, an absence of which will cause superficial gastric ulcers in chicks, is well recognized by persons interested in the nutrition of poultry.<sup>1</sup> Members of the medical profession at large hardly seem aware of this factor and of the significant fact that definite gastric lesions may be produced experimentally, at least in chicks, by dietary means alone. Of perhaps even greater significance is the recent demonstration that the same type of erosive lesion may be produced by feeding cinchophen, which will cause not only superficial ulcers but the severer types of gastric ulceration encountered in man, including deep penetration and perforation.<sup>2</sup> These cinchophen gastric ulcers differ only in degree from ulcers produced by a deficient diet alone, and they may also be prevented or modified by a dietary factor.

As this important relation exists between these two apparently etiologically different types of experimentally produced gastric ulceration, the present knowledge of the deficiency type has been reviewed and supplemented and in addition further studies are reported concerning the development and the alleviation of cinchophen gastric ulcers themselves.

## METHOD

White leghorn baby chicks were used for all the experiments.<sup>3</sup> These chicks were hatched in Petaluma and were received in the laboratory the day of hatching or the subsequent day. They were given a starter mash diet for a few days before being transferred to the experimental diets. They were raised indoors in brooders with screen floors.

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From the Department of Medicine, Stanford University School of Medicine.

This investigation was aided by a grant from Eli Lilly and Company, Indianapolis.

1. (a) Dam, H.: Antihæmorrhagic Vitamin of Chick, *Biochem. J.* **29**:1273, 1935. (b) Dam, H., and Schonheyder, F.: Occurrence and Chemical Nature of Vitamin K, *ibid.* **30**:897, 1936. (c) Almquist, H. J., and Stokstad, E. L. R.: Dietary Haemorrhagic Disease in Chicks, *Nature, London* **136**:31, 1935; (d) Gizzard Factor of Chick, *J. Nutrition* **13**:339, 1937. (e) Almquist, H. J.: Source and Nature of Gizzard Factor, *ibid.* **14**:241, 1937. (f) Esselen, W. B.: Nutritional Gizzard Lesions in Chicks, *Poultry Sc.* **18**:201, 1939.

2. Cheney, G.: Effect of Diet and Cinchophen on Production of Experimental Gastric Ulcers in Chicks, *Proc. Soc. Exper. Biol. & Med.* **45**:190, 1940.

3. The Poehlmann Hatchery, Petaluma, Calif., supplied all the birds used.

TABLE 1.—Effect of Dietary Supplements on Cinchophen Peptic Ulcers in Chicks

Series No.	Diet	Supplement	Cinchophen, per Cent	No. of Chicks	Ago at Autopsy, Days	Average Weight at Autopsy, Gm.	Grade of Ulceration	Interpretation
S-5-2	Basal diet, see text	None.....	None	5	20	178.8	1.3	Control
S-5-3		None.....	0.5	8	21	151.6	2.1	Control fed cinchophen
S-5-5		5% dried leaves of cereal grasses.....	0.5	8	22	175.0	1.46	Protective
S-5-7		10% dried leaves of cereal grasses.....	0.5	8	23	171.6	1.5	Protective
S-5-4		None.....	1.0	8	21	120.0	3.63	Control fed cinchophen
S-5-8		5% dried leaves of cereal grasses.....	1.0	10	22	101.8	2.4	Protective
S-5-10		10% dried leaves of cereal grasses.....	1.0	10	21	131.2	2.3	Protective
S-6-1A	Basal diet plus 10 per cent alfalfa	None.....	None	11	22	179.7	1.0	Control
S-6-1		None.....	1.0	12	20	111.7	2.67	Control fed cinchophen
S-6-5		20% spinach, wet.....	1.0	8	20	101.1	3.25	No protection
S-6-6		Milk ad lib.....	1.0	8	19	138.0	1.13	Protective
S-6-7		2% of a combination of sodium glycocholate and sodium taurocholate	1.0	8	19	112.5	2.5	No protection
S-6-8		5% $AlO_3$ .....	1.0	8	20	101.8	3.37	No protection
S-6-3	Vitafood, see text	Chick liver, 2.5 Gm. per bird daily.....	1.0	6	17	116.0	3.2	No protection
S-6-2A		Chick liver, 2.5 Gm. per bird daily *.....	1.0	4	17	121.6	2.1	? Protective
S-6-2		Dog liver, 2.5 Gm. per bird daily.....	1.0	10	18	139.9	1.75	Protective
S-6-4		Dog liver, 10 Gm. per bird daily.....	1.0	10	18	130.9	2.2	Protective
S-1-3		None.....	None	10	22	208.0	0.25	Control
S-1-1		None.....	0.5	8	21	163.4	0.25	Control fed cinchophen
S-1-5	Vitafood, see text	Dog liver, 2.5 Gm. per bird daily.....	0.5	10	21	181.5	0.15	? Protective
S-1-8		None.....	1.0	8	21	143.3	0.61	Control fed cinchophen
S-1-6		Dog liver, 2.5 Gm. per bird daily.....	1.0	10	21	157.9	0.25	Protective
S-1-1		Human liver, 2.5 Gm. per bird daily.....	1.0	10	21	182.6	0.38	Protective
S-1-9		2% cholic acid.....	0.5	10	22	157.0	0.33	No protection
S-1-10		2% cholic acid.....	1.0	10	22	139.3	0.92	No protection
S-1-7		5% mucin.....	1.0	8	22	132.8	1.28	No protection
S-2-1		Gastron, 3.3 cc. per bird daily.....	None	8	21	171.5	0.41	Control given gastron
S-2-2		Gastron ad lib.....	None	8	10	40.6	?	(See text)
S-1-2		Gastron, 3.3 cc. per bird daily.....	1.0	10	21	121.4	1.35	No protection
S-3-1	Vitafood heated 6 hours at 80 C.	None.....	None	10	23	.....	0.2	Control
S-3-4		None.....	1.0	10	23	161.1	1.95	Control fed cinchophen
S-3-3		Dog liver, 2.5 Gm. per bird daily.....	1.0	10	23	145.9	1.6	Protective
S-3-5		Dog liver, 2.5 Gm. per bird daily †.....	1.0	10	23	145.0	2.3	No protection
S-3-7		Dog liver, 2.5 Gm. per bird daily †.....	1.0	10	23	153.0	2.1	No protection
S-3-6		Evaporated milk.....	1.0	10	23	153.5	1.05	Protective

\* Livers from cinchophen-fed birds.

† Livers from cinchophen-fed dogs.

Each group of chicks ordinarily was made up of 8 to 10 birds. These experimental groups were started in the second week of life when they were first weighed. Autopsy studies were usually carried out between the seventeenth and the twenty-third day. Cinchophen was fed seven to fourteen days preceding autopsy. The weights of the birds were recorded again before and after cinchophen

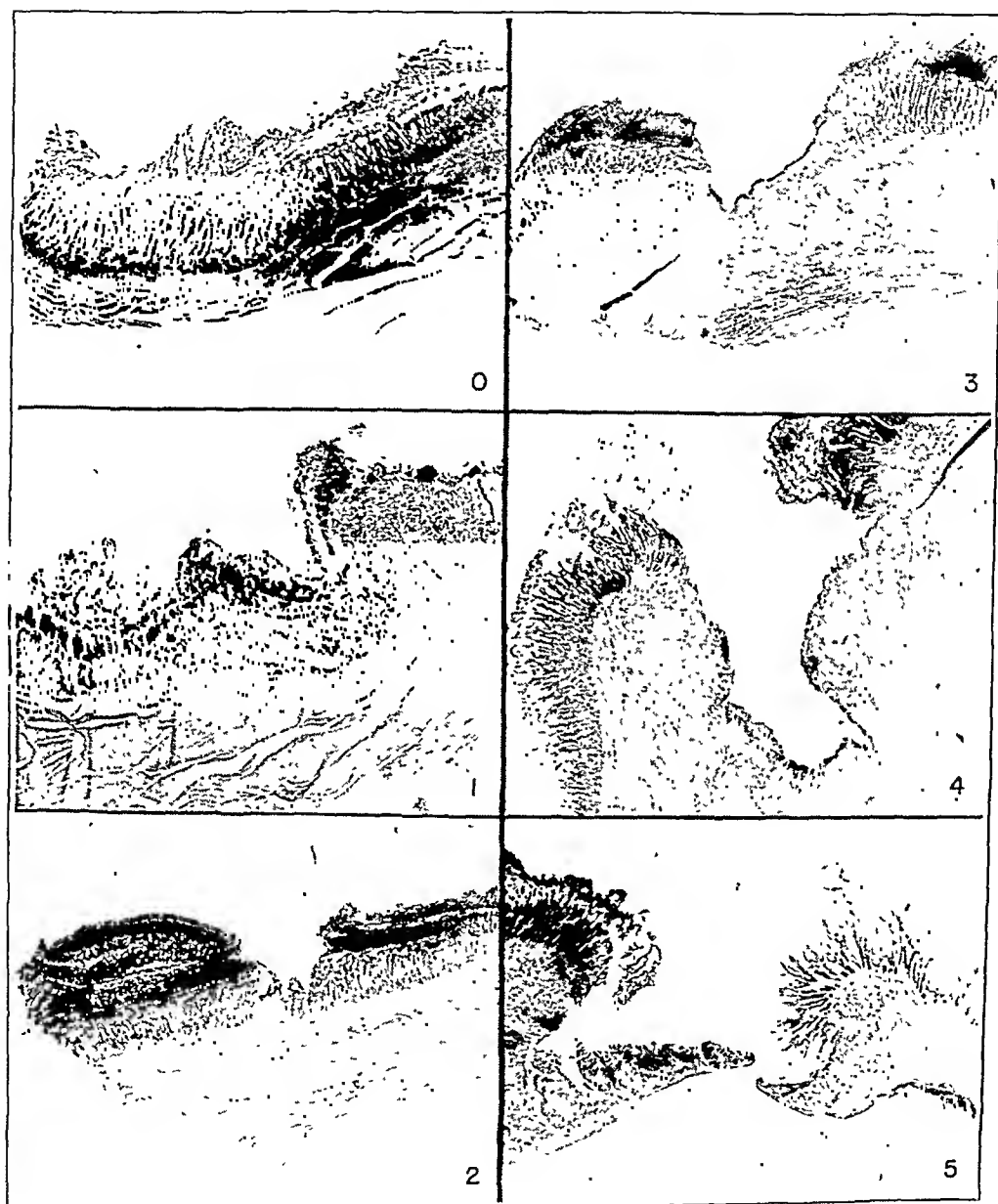


Fig. 1.—Cross sections of chick stomach walls illustrating the method used for scoring different grades of ulceration. 0, normal wall; 1, the initial lesion, a mucosal hemorrhage beneath the chitinous lining of the gastric lumen; 2, superficial erosion with loss of the chitinous layer and flattening of the mucosa; 3, a peptic ulcer with destruction of the mucosa and with a flat base; 4, a penetrating ulcer with invasion of the muscle layers, and 5, a perforating ulcer with peritonitis.

feeding. The special diets were started the third to the fifth day of life, and additional substances to be tested for their protective value against ulceration were added to the diet for a five day period before cinchophen was administered. These substances when dry were thoroughly mixed with the diets; otherwise they were offered separately. A control group of birds was run with each type of diet for each series.

The basal diet previously described was used again.<sup>4</sup> It consists of ether-extracted or gasoline-extracted fish meal 17.5 per cent, brewers' yeast 7.5 per cent, sodium chloride 1 per cent, cod liver oil 1 per cent and rice flour 73 per cent. This diet has repeatedly been shown to be deficient in the anti-gizzard-erosion factor and is also deficient in vitamin K. The diet designated in figure 2 as 2 *A* and in table 1 as *B. D. A.* is the same diet plus 10 per cent alfalfa to add bulk. This diet is also deficient, but the incidence of erosions is lower. A commercially prepared mash known as vitafood marketed by the Poultry Producers of California offers

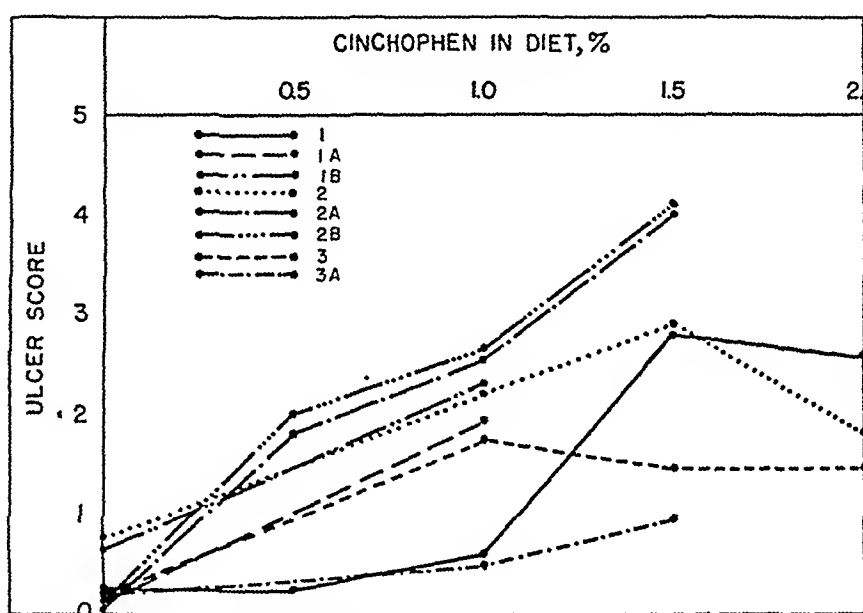


Fig. 2.—Relation of the type of diet and the percentage of cinchophen fed to the grade of gastric ulceration in chicks. 1, a protective diet; 1 *A*, the same diet heated six hours at 80 C.; 1 *B*, the same diet heated twenty-four hours at 80 C.; 2, a deficient nonresidual diet; 2 *A*, the same diet plus 10 per cent alfalfa; 2 *B*, the same diet plus 25 per cent alfalfa; 3, a high carbohydrate protective diet, and 3 *A*, a high carbohydrate nonresidual diet.

a well balanced diet which has proved protective against gastric ulcers. It consists of protein 18.5 per cent, fat 3.7 per cent, carbohydrate 66.5 per cent, ash 5.8 per cent, fiber 3.8 per cent and minerals (calcium, phosphorus and manganese) 2.1 per cent. It contains 5 per cent dehydrated alfalfa and 0.25 per cent sardine oil fortified with vitamin A. This diet has served satisfactorily as a normal control type of feed.

All birds were autopsied at the end of the series, on the same day if possible. The condition of each gizzard was carefully noted, and the degree of ulceration was observed in the fresh specimen and scored as previously described.<sup>2</sup> The grades of ulceration are shown in figure 1. Grade 1 represents the earliest

4. Cheney, G.: Gastric Acidity in Chicks with Experimental Gastric Ulcers, *Am. J. Digest. Dis.* 2:104, 1938.

demonstrable lesion, a mucosal hemorrhage without rupture of the chitinous lining of the gizzard. In lesions of grade 2, rupture has taken place, part of the mucosa is thinned out or destroyed, the evidence of bleeding may disappear and a typical superficial gastric ulcer, or area of gizzard erosion, is present. In lesions of grade 3, the mucosa has largely disappeared and the ulcer has a flat base with punched-out appearance and often with thickened indurated margins. Lesions of grade 4 represent definite penetration into the underlying muscle layers, and those of grade 5, perforation with involvement of the peritoneum. If the exact grading is in doubt, the lesion is scored half way between two grades. For example, if there is a question whether the muscle layer is or is not invaded (grade 4 or grade 3), the lesion is scored as 3.5. At first microscopic sections were made to determine the exact depth of an ulcer, but with experience gross observation of a cross section of the lesion has proved reasonably accurate.

#### PRODUCTION OF LESIONS

Cinchophen was fed in concentrations of 0.5, 1, 1.5 and 2 per cent thoroughly mixed with the diet. It was soon noted that the 2 per cent level was often so toxic that few birds survived the experiment. Toxic symptoms consisted of weakness, loss of coordination, loss of appetite, marked prostration and occasionally death within twenty-four or forty-eight hours. Ordinarily, the 1 per cent level produced fairly satisfactory gastric lesions without too great toxicity and without causing death of the birds. All the birds fed this amount of cinchophen failed to gain weight as well as the controlled groups, however. The relation of the percentage of cinchophen fed to the production of ulceration is well shown in figure 2. The ulceration becomes progressively more severe as a rule up to the 1.5 per cent level but may be less severe after that in birds surviving the experiment because so little feed is taken. Although it varies with the type of diet fed, the general trend is constant. One half of 1 per cent cinchophen usually produces lesions, but few are more severe than grade 2.

The production of lesions by feeding cinchophen will vary greatly with the type of diet given because of the varying amounts of protective substance contained in the diets, because of the amount of roughage and possibly also because of the carbohydrate content. Figure 2 depicts the varying effects of the diet on the grade of ulceration. An adequate protective diet shows an almost complete absence of lesions in the control experiments and no marked increase until more than 1 per cent of cinchophen is fed. In contrast to this, chicks on a deficient diet show some lesions in the control group and pronounced lesions at the 0.5 per cent level. In chicks on the high carbohydrate protective and non-residual diets only mild ulceration occurred, and in one series (fig. 2 3 A) the degree of ulceration in birds fed 1 per cent cinchophen was not as great as that in the control groups on a deficient diet without cinchophen.

Figure 2 also shows the effect of heat on the protective diet. When this diet is heated at 80 C. for six hours, a marked deficiency is manifest when cinchophen is fed, compared to the lesions produced by the same diet without heating. When this diet is heated at 80 C. for twenty-four hours, the deficiency is slightly more pronounced.

When the diet is finely divided, it is evident that cinchophen may be less well retained and consequently toxic effects may be less severe. On the contrary, a bulky diet is retained longer and cinchophen intoxication and gastric ulceration become more marked. This is shown in figure 2 by comparing the degree of ulceration produced by a deficient nonresidual diet and that produced by the same diet to which alfalfa has been added. This is most obvious at the 1.5 per cent level. At this level the grade of ulceration is 2.9 without alfalfa but is 4.0 when 10 per cent alfalfa is added and is 4.1 when 25 per cent is added, despite the protective value of alfalfa meal when it is fed liberally.

The importance of the diet in producing lesions is best understood by noting the marked differences of effect of the same amount of cinchophen when the different feeds contain various amounts of the protective substance. At the 0.5 per cent level the degree of ulceration varies between 0.25 and 2. At the 1 per cent level it varies between 0.5 and 2.65. At the 1.5 per cent level it varies between 0.95 and 4.1. In the 3 experiments at the 2 per cent level, it varies between 1.45 and 2.6. However, as already noted, the degree of ulceration is fairly consistent for a given diet at a given level of cinchophen. This was noted repeatedly in feeding 1 per cent cinchophen to different series of chicks when each group fed was on the same diet.

#### PATHOLOGIC OBSERVATIONS

Grossly the gastric lesions vary greatly in form, as indicated by the method of grading the severity of the ulceration, shown in figure 1. The earliest noticeable change is a darkly stained area visible beneath the chitinous layer, which in cross section represents a hemorrhage into the gastric mucosa. This area of bleeding may be only a millimeter in diameter or may be diffuse and extensive. It may be localized to several different areas. It is best seen in the lesions due to dietary deficiency alone and particularly in birds which are also deficient in vitamin K. Actual erosions with loss of the chitinous layer over an area of thinned-out mucosa are the common lesions encountered and may vary considerably in size and number. They may be classified as superficial ulcers, although no real tissue necrosis has taken place. As the lesion becomes deeper, it may assume various forms, appearing funnel shaped, triangular, punched out or, not infrequently, flat based with rolled and

indurated edges, as shown in figure 3. As penetration through the mucosa into the muscle layers occurs, the ulcer appears grossly identical with the peptic lesions so well described in human beings. There is no evidence of gastritis associated with these ulcers.

An ulcer existing a number of days or perhaps a week may be almost pinpoint in size or may appear as an extensive area of roughening, presenting a "chewed-up appearance" of the inner lining. Large ulcers



Fig. 3.—A typical large ulcer of grade 3 with a flat base and indurated margins. It is in the muscular part of the bird's stomach (gizzard) just below the fundus, a common site.

1 cm. in diameter occasionally occur, but the average erosion is somewhat irregular in outline and commonly covers a surface a few millimeters in diameter. Deep penetrating ulcers are more likely to be small in appearance than large.

Usually more than one lesion is evident in a stomach which is affected, but different grades of ulceration may occur in the same organ. A group

of 69 chicks was studied from the point of view of incidence of single and multiple lesions and the severity of ulceration occurring. All of these chicks were fed on the basal diet containing 10 per cent alfalfa to which 0.5 or 1 per cent cinchophen had been added. The average ulcer score for the whole group was 2.78. Only three stomachs were free from lesions. Of the 66 stomachs in which lesions were found, there were only single ulcers in 18, or 27.3 per cent, while the rest showed two or more ulcers. Fifteen showed two; 10 showed three; 7 showed four, and in the remaining 16 there were more than four lesions per stomach. In the 53 stomachs in which the number of lesions was counted there were one hundred and six ulcers. If one graded the individual stomachs according to the severest lesion found, there were seven lesions of grade 1, thirty of grade 2, fifteen of grade 3, ten of grade 4, and four of grade 5. It is noteworthy that all four of the perforating ulcers and four of the penetrating ones were single lesions. Occasionally, a single stomach would show two or three grades of lesion, and rarely a lesion of grade 1 and one of grade 4 or 5 would be present in the same stomach wall.

It is a striking feature that the vast majority of lesions are limited to the submarginal area, that is, just below the juncture of the chitinous lining of the gizzard with the smooth mucous membrane-lined intermediate zone which connects the upper glandular fundus, or proventriculus, with the lower, muscular part of the stomach. This area is where the acid, pepsin-containing juice of the fundus first strikes the lining of the gizzard. Not infrequently superficial lesions occur in the distal pouch of the gizzard, where acid gastric juice enters freely. However, no penetrating or perforating ulcers have been noted in this distal region.

As previously pointed out, ulcers do not occur in the fundus of the stomach or in the intermediate zone. They appear only in the muscular portion of the stomach, which does not secrete acid or pepsin. No lesions have ever been noted at the duodenal orifice, but in the chick the duodenum leaves the gizzard at a right angle, some distance below the submarginal area, and consequently is not bathed by acid gastric juice.

Occasionally, ulcers not only penetrate the muscular layer but perforate through the serous lining into the peritoneal cavity. This has never been observed in lesions due to dietary deficiency alone. The penetration most commonly occurs just below the intermediate zone and not infrequently into the liver bed. Penetrating ulcers are sometimes small and may be difficult to visualize from the side of the gastric lumen without making a cross section of the stomach wall. Perforation has been noted as early as the fifth day of cinchophen feed-



ing, and, as already pointed out, the perforating lesion is not infrequently the only one occurring. When perforation occurs, a localized abscess with peritonitis may form or diffuse peritonitis may occur with fluid collection and abdominal distention. In 1 sick chick a large gas bubble could readily be observed through the distended abdominal wall indicative of a pneumoperitoneum. At autopsy this bird had a peritoneal cavity distended with gas and fluid and a perforating ulcer approximately 1 mm. in diameter.



Fig. 4.—Multiple stomach ulceration, grade 5, with one perforating lesion.

Histologically, the superficial lesions show changes in the chitinous layer and gastric mucosa which have already been carefully described.<sup>5</sup> I have verified these repeatedly. As the ulcers become deeper, and particularly when they penetrate the muscle layer, the same characteristic histologic changes develop which occur in peptic ulcers in human

5. Lansing, A. I.; Miller, D., and Titus, H. W.: The Formation of Erosions of the Gizzard Lining in the Young Chick, *Poultry Sc.* 18:475, 1939. Esselen.<sup>11</sup>

beings. There are tissue edema and necrosis with vascular engorgement and extensive polymorphonuclear leukocytic infiltration. Also an infiltration with eosinophils is common in the advanced lesions. An increase in fibroblasts occurs below the base of the ulcer. These changes are well depicted in figure 5, which shows a deeply penetrating large gastric

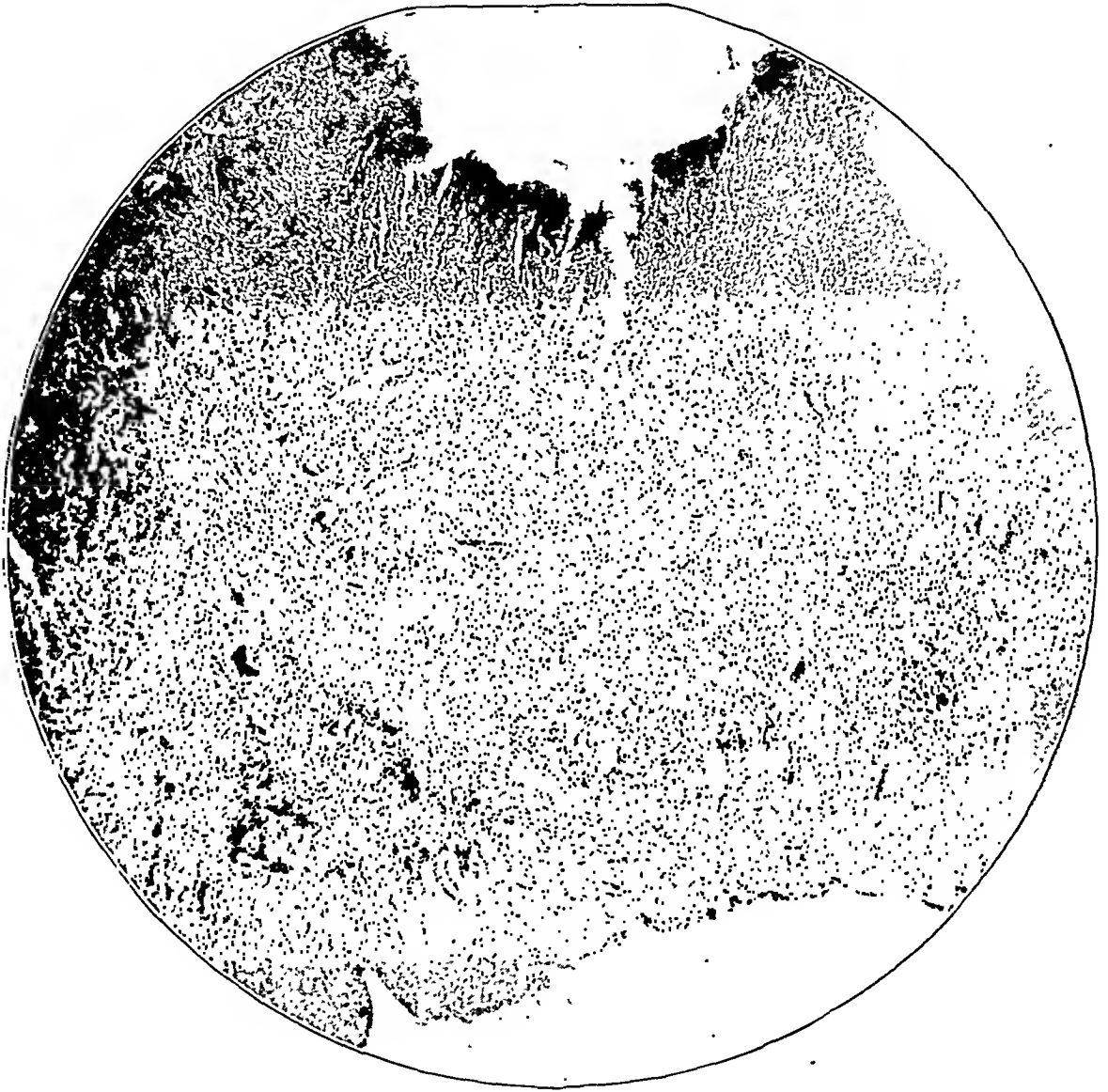


Fig. 5.—A photomicrograph of a penetrating subacute ulcer of grade 4, with an overhanging margin and a necrotic base beneath which is granulation tissue. There is a pronounced infiltration of polymorphonuclear leukocytes and eosinophils.

ulcer from a bird fed cinchophen one month before it was autopsied. The late effects of chronicity and partial healing have not been studied, as the chicks have not as yet been kept under observation sufficiently long to afford a proper opportunity.

## DEVELOPMENT AND COURSE OF ULCERATION

The development of gastric ulcers will vary not only with the type of diet fed but with the age and parentage of the bird. When newly hatched chicks are raised on a deficient diet, erosions begin to appear during the second week of life and are most pronounced by the third and the fourth week, when they are usually present in 90 to 100 per cent of the birds. As the birds grow older, evidence of the deficiency becomes progressively less marked.<sup>4</sup> Chicks reared on an adequate diet during the first month and then placed on a deficient diet rarely show pronounced lesions. Occasionally, an embryo chick, a newly hatched chick or an older bird on the usual practical diet may show erosion of the gizzard.<sup>6</sup> Chicks from hens kept on a deficient diet will show lesions earlier in life than chicks from well fed hens.<sup>7</sup>

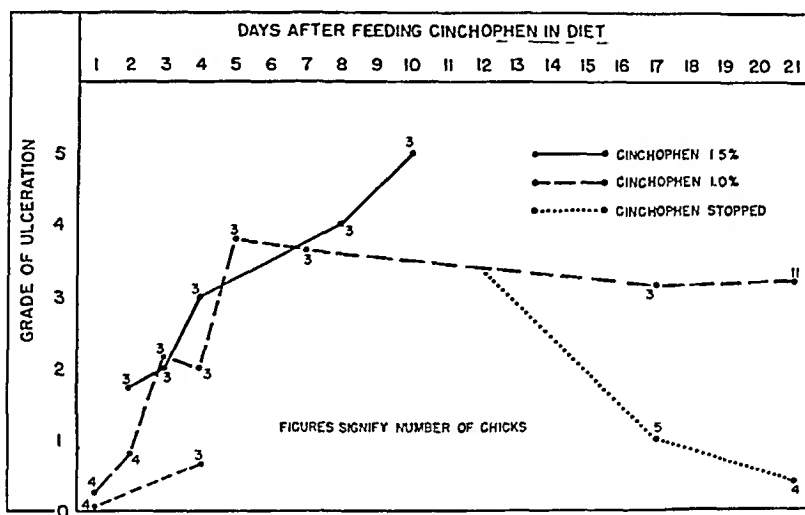


Fig. 6.—The development of gastric ulceration in chicks when 1 per cent cinchophen (broken line) and 1.5 per cent cinchophen (continuous line) are added to a basal diet including 10 per cent alfalfa and when 1 per cent cinchophen (chain line) is added to the same basal diet including 25 per cent alfalfa. Rapid improvement (dotted line) occurred after cinchophen feeding was stopped.

When cinchophen is added to the diet during the second week of life, the onset of ulceration will vary not only with the type of diet used but with the amount of cinchophen fed. Repeated observations of chicks on varying diets containing 1 per cent cinchophen reveal no more evidence of gastric ulceration twenty-four hours after cinchophen feeding is started

6. (a) Almquist, H. J., and Stokstad, E. L. R.: A Nutritional Deficiency Causing Gizzard Erosions in Chicks, *Nature*, London **137**:581, 1936. (b) Jungheer, E.: Bulletin 202, Connecticut Agricultural Experiment Station, 1935, p. 52.

7. Almquist, H. J.: Personal communications to the author.

than might be attributed to a deficient diet alone, although many of the birds show obvious toxic symptoms. Of the 8 birds autopsied the day after the experiment in figure 6 was started, only 1 showed a lesion, and this was without ulceration (grade 1). Also, only 1 of the 4 birds autopsied after the second day showed a lesion, and this was of the same type. It is evident from these observations that the gastric lesions do not develop as a direct result of toxic action of the cinchophen on the gastric lining but as a late and possibly indirect effect. Feeding cinchophen at the 1.5 per cent level produces ulceration earlier and in a more severe form.

In figure 6 the effects of feeding cinchophen at the 1 and the 1.5 per cent level in different series of birds is compared. The series receiving 1 per cent cinchophen was started at 10 days of age and the series receiving 1.5 per cent at 13 days. Both received the basal diet plus 10 per cent alfalfa. Small groups of birds were autopsied at intervals, as shown on the chart. Of those receiving the larger amount of cinchophen, all showed lesions after the second day, and the degree of ulceration steadily advanced, until after ten days the 3 birds studied all had perforated ulcers (grade 5). The degree of ulceration in the birds receiving 1 per cent cinchophen advanced to an average grade of ulceration of 3.8 in 3 birds after five days, including 1 bird with a perforated ulcer and peritonitis. The degree of ulceration diminished somewhat during the next sixteen days, averaging slightly over 3. On the twelfth day of feeding cinchophen was removed from the diet of 9 of these birds, and five days later 5 birds were autopsied. All showed lesions so slight that they were interpreted as healing. Only 1 showed any definite erosion. The average grade was only 1. The remaining 4 birds were autopsied four days later. Two showed no lesions, and 2 showed only questionable lesions. It is obvious that rapid healing of ulceration occurs when cinchophen is removed from the diet. This corresponds to the improvement already reported in lesions produced by a deficient diet alone when the deficiency is rectified.<sup>8</sup>

Figure 6 also shows that lesions develop more slowly when a protective diet is fed to which 1 per cent cinchophen is added. Seven 11 day old birds were fed on a basal diet to which 25 per cent alfalfa had been added instead of 10 per cent. Autopsies of 4 birds not only failed to show lesions after the first day, but the 3 remaining birds killed after four days did not show gastric ulceration. Two had mucosal hemorrhages. The average grade for the 3 birds was only 0.67.

8. Cheney, G.: Gastro-Enterology in 1936: Selected Topics, Arch. Int. Med. 60:705 (Oct.) 1937.

## THE PREVENTIVE SUBSTANCE

The protective substance which has been known as the anti-gizzard-erosion factor was originally thought to be identical with vitamin K. In the earlier experiments with diets deficient in this antihemorrhagic vitamin gizzard erosions were almost constant and were considered one of the cardinal manifestations of the deficiency. The bleeding tendency produced lesions of the gastric lining grossly simulating a hemorrhagic erosive gastritis and occasionally single gastric ulcers with severe and even fatal hemorrhage. However, five years ago Almquist and Stokstad<sup>9</sup> clearly showed that the stomach erosions were not dependent on vitamin K deficiency. In the presence of adequate amounts of all the known vitamins in a vitamin K-deficient diet the erosions still occurred, even when vitamin K was administered in its natural form. I have repeatedly confirmed these observations by adding synthetic forms of vitamin K to vitamin K-deficient diets and noting the same incidence of ulceration as when no vitamin K had been added. This necessitated postulating the presence of an additional substance or factor closely associated with K. Almquist and Stokstad<sup>10</sup> have shown that it is a fat-soluble sterol, but unlike vitamin K it is in the saponifiable fraction.

A variety of substances have been tested for the presence of this factor. The results presented have been derived from the publications of Almquist and Stokstad,<sup>11</sup> from personal communications with Almquist,<sup>7</sup> from articles by Dam and Schonheyder<sup>12</sup> and by Bird and his co-workers<sup>13</sup> and from heretofore unpublished experiments of mine. Alfalfa meal is a known standard source of protection, but its effect is complete only when it is fed at the 20 to 25 per cent level of diet. Different lots of alfalfa vary considerably in potency. Fresh kale and kale extract are highly effective at the 5 per cent level. Hempseed meal is protective at the 10 per cent level. Dried hog liver is protective at the 20 per cent level,

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9. Almquist and Stokstad (footnotes 1 *d* and *e* and 6 *a*).

10. Almquist, H. J.: The Effect of Hemp Seed Preparations and of Fineness of Diet on the Chick Gizzard Lining, *Poultry Sc.* **27**:155, 1938; footnote 1 *e*.

11. Almquist and Stokstad (footnotes 1 *c* and *d*). Almquist.<sup>10</sup>

12. Dam, H.: Hemorrhages in Chicks Reared on Artificial Diets: New Deficiency Disease, *Nature, London* **133**:909, 1934. Dam, H., and Schonheyder, F.: A Deficiency Disease in Chicks Resembling Scurvy, *Biochem. J.* **28**:1355, 1934. Footnotes 1 *a* and *b*.

13. Bird, H. R.; Oleson, J. J.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: Relation of Grit to the Development of the Gizzard Lining in Chicks, *Poultry Sc.* **16**:238, 1937. Bird, H. R.; Kline, O. L.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: The Distribution and Properties of the Anti-Gizzard-Erosion Factor Required by Chicks, *J. Nutrition* **12**:571, 1936.

and hog liver fat and certain fractions of it are protective when they constitute as little as 3 per cent of the feed. Clarified wheat bran oil is effective when as little as 1.37 per cent is fed in the diet.

A number of substances commonly used in the diet of human beings have been shown to contain this factor. Wheat bran is protective when it comprises 30 per cent of the diet and so is barley bran at the 62 per cent level. Other foods are cooked spinach 20 per cent; canned mixed greens 0.5 per cent dry weight; dried leaves of cereal grasses (cerophyl) 1 per cent; certified raw whole milk, pasteurized whole milk, buttermilk and 20 per cent cream fed in place of water; raw egg yolks when fed in the proportion of  $\frac{1}{8}$  yolk per chick per day for fourteen days; olive oil 10 per cent; fresh tomatoes ad libitum, and soy bean oil 10 per cent.

The following wide variety of substances has been shown to be completely or relatively impotent under the experimental feeding condition carried out: rice flour and bran; sardine meal; casein; brewers' yeast; ground barley, yellow corn, oats and rye; soy bean meal; peanut meal; sesame meal; linseed meal; black and white sunflower seed; orange meal; cod liver oil; wheat germ oil; copra, soya bean, rapeseed and linseed oil and oil of orange; dried skim milk; dried whole milk; dried chicken livers; hard boiled eggs (twenty minutes), yolk and white; fresh lemon juice; fresh yellow carrots; fresh lettuce and fresh spinach; fresh green peas; artichokes; papaya; garlic; canned tomato juice; lard; avocados; dilute, concentrated and dry liver extracts given by mouth and sterile liver extracts administered by injection; dried calf brain; dried ox muscle; dried ox tongue, and dried calf thymus.

Other substances tried out for protective potency and found wanting are cholesterol, phytosterol, carotene, yeast sterols, alpha tocopherol, phytol, glucuronic acid, acacia, agar, choline, creatine, phytic acid, aloin, linoleic acid, copper sulfate, sodium acid phosphate, glycerine, cotton pulp and sand.

The use of stomach extracts has been most enlightening. Almquist fed dried normal chicken gizzard linings at the 5 per cent level, which gave excellent protection, while diseased linings from chickens on a deficient diet were not effective. I found dried whole hog stomach extract and normal human gastric mucosa dried at 37 C. protective both at the 1 per cent and at the 5 per cent level. Only 1 of 8 birds fed on a deficient diet plus a supplement of 5 per cent hog stomach mucosa had a gastric lesion, giving an ulcer score of 0.25; while lesions developed in 6 of 9 birds receiving a 1 per cent supplement, giving a score of 0.89. Lesions developed in all of 11 birds of the control series without hog mucosa. The ulcer score was 1.7 per cent. A commercial preparation of hog stomach extract (ventriculin) was fed as a 5 per cent supplement to 8 birds, and lesions developed in 4, giving an ulcer score of 0.75. As

the control score for this experiment was 1.13, the margin of protection was not so pronounced as with the first series. Almquist and Mecchi<sup>14</sup> reported negative results with dried stomach lining but did not state the source of their material, the method of drying or the amounts fed.

Similarly, 7 birds were fed 5 per cent normal human gastric mucosa as a supplement, in none of which lesions developed; while lesions occurred in 4 of 6 birds fed a 1 per cent supplement, giving a score of 0.83. The results for the control group were the same as those obtained with hog mucosa extract.

A commercial extract of pepsin fed at the 5 per cent level failed to produce any effect on the incidence of gastric lesions when fed alone or with 0.1 per cent of dilute hydrochloric acid administered in the drinking water. Higher concentrations of acid tended to cause gastric mucosal hemorrhages, general intoxication and frequently an early death.

A number of therapeutic agents commonly employed in treating peptic ulcers in human beings were administered to chicks on a diet deficient in the anti-gizzard-erosion factor. The only one which may have been successful was powdered aluminum hydroxide fed at the 5 per cent level. The grade of erosion in 5 birds was low, 0.3, but the control group in this series showed an ulcer sore of only 0.75. Soda bicarbonate 1 per cent, magnesium trisilicate 5 per cent, gastric mucin 10 per cent, gelatin 5 per cent and daily injections of 0.1 cc. of histidine for twenty-one days failed to protect the birds from lesions.

The protective substance is readily destroyed by heat. This was first demonstrated by Almquist and Stokstad in 1937.<sup>14</sup> It was shown that preparations of dried kale heated at more than 100 C. for twenty-four hours lost completely their power to prevent gizzard erosions. Also soy bean oil and wheat bran, which afford fair protection at the 10 per cent level, failed to protect when heated at 120 C. for twenty-four hours. In 1938 I found that although fresh egg yolks offered good protection against gastric erosion due to dietary deficiency, three-minute boiled yolks offered less protection and yolks boiled for twenty minutes offered poor protection. The relative ulcer scores for a group on each of these three experimental foods were 0.35 (control 1.9), 0.5 (control 1.10) and 1.23 (control 2.0). Similarly, boiled milk was ineffective in comparison to fresh and pasteurized milk.

The effect of heat at 80 C. on the vitafood diet has already been pointed out (fig. 2). Unheated this diet was highly protective, as only 1 bird in 6 showed a superficial gastric lesion, with an average grade of ulceration for the group of 0.25, and even when 1 per cent cinchophen

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14. Almquist, H. J., and Mecchi, E.: Influence of Bile Acids, Vitamin K and Cinchophen on Erosions of the Chick Gizzard Lining, *Proc. Soc. Exper. Biol. & Med.* 46:168, 1941.

was added, only 4 of 8 birds showed lesions, with a score of 0.61; all of these lesions were superficial. When this same diet was heated six hours at 80 C., it did not prove more deficient, the grade of ulceration being 0.2 for 10 birds, only 2 showing superficial lesions. However, this heated diet had lost its latent reserve power of protection, for when 1 per cent cinchophen was added lesions developed in all 10 birds, with an average grade of 1.95, which is more than three times as pronounced as when the diet was unheated.

Heating the vitafood diet twenty-four hours at 80 C. proved even more destructive to the protective factor. Lesions developed in 5 of 8 birds on this heated diet without cinchophen. The grade of ulceration was 0.63. When cinchophen was added at the 1 per cent level, all 7 birds in the group fed showed lesions, one of which was of the punched-out type and one was penetrating deeply into the muscular layer. The average score of the lesions was 2.29 to be compared to 0.61 without heat and 1.95 when the period of heating was eighteen hours shorter.

#### THE PROTECTIVE SUBSTANCE AND CINCHOPHEN ULCERS

It has already been pointed out in discussing the production of gastric ulcers by cinchophen that a certain type of diet, such as vitafood, may be much more protective than another, such as the basal diet containing alfalfa. The efficacy of a few specific food substances in regard to this protective capacity has been noted in a previous communication.<sup>2</sup> It was shown to be present in dried leaves of cereal grasses, canned mixed greens and milk. Further studies along similar lines have been carried out, and the results are recorded in table 1. The majority of food substances tested fall into three general groups: greens and milk; various forms of fresh liver, and stomach extracts.

The effect of dried leaves of cereal grasses was tried out again. It was added at the 5 per cent and the 10 per cent level to the basal diet containing 0.5 per cent and 1 per cent cinchophen. Table 1 shows that it proved protective against both 0.5 and 1.0 per cent cinchophen as compared to the controls but that the 10 per cent level was no more effective than the 5 per cent level. Twenty per cent canned wet spinach was not effective against the basal diet with alfalfa which contained 1.0 per cent cinchophen, although the diet was not relished, and consequently the birds received less cinchophen than the control group. Due to the bulk of the diet, the cinchophen may well have been retained longer and proved more toxic. This is also suggested by the poor gain in weight of this group. Fresh milk in place of water added to the same diet gave good protection as did evaporated milk diluted to its original volume. However, it must be noted that birds allowed to drink milk freely eat less of the diet than



the control birds and consequently receive somewhat less cinchophen. Almquist and associates<sup>15</sup> have recently confirmed the protective properties of milk.

Fresh liver was fed separately from the mash to ten groups of chicks which were receiving 1.0 per cent cinchophen. The liver therapy was started five days before feeding cinchophen and was continued throughout the experiment, usually for a total period of two weeks. The liver was preserved frozen at  $-10^{\circ}\text{C}$ . and only thawed out immediately before it was offered to the birds each day. The dose was 2.5 Gm. per bird in all but 1 experiment, when 10 Gm. per chick was fed. The chick livers used in group S-6-2A were from month old birds which had received 1 per cent cinchophen in the diet for twenty-one days. The dog liver used in group S-3-5 was from 2 adult dogs which had received 0.2 Gm. of cinchophen per kilogram of body weight daily for seventeen and twenty-five days before death, and that used in group S-3-7 was from 2 dogs on the same dose which were killed on the twenty-ninth day of cinchophen feeding.

The normal chick liver was not protective. In the table it looks as if liver from chicks treated with cinchophen might have been protective, as the ulcer score of 2.1 was less than the 2.67 score of the controls. However, the number of birds in group S-6-2A was too small to afford a basis for any such conclusion. It is evident that dog liver is definitely protective, although not strikingly so. The group of chicks receiving 10 Gm. of liver per bird was probably better protected than that receiving 2.5 Gm. and better protected than the table indicates, as 1 per cent of cinchophen was added to the liver in this experiment in addition to that which was added to the mash diet. This addition was considered justifiable as these birds ate proportionately less mash because of the large amounts of meat ingested, but this also meant that more cinchophen was eaten than in the other groups. The two groups of birds fed liver from cinchophen-treated dogs showed no evidence of protection compared to the control group without liver, the ulcer scores being slightly higher, while the birds in this series receiving liver from dogs not treated with cinchophen showed a definite, although slight, reduction in the degree of ulceration. The grade for this series was 1.6 compared to the control grade of 1.95. Group S-1-4 fed human liver appeared to be definitely protected, with an ulcer grade of 0.38 compared to the control of 0.61, but the difference in these figures is not sufficient to make certain of this point without studying a larger group of birds and having a control group with more severe lesions.

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15. Almquist, H. J.; Mecchi, E., and Kratzer, F. H.: Effect of Milk on Gizzard Erosion and Cholic Acid in the Chick, *Proc. Soc. Exper. Biol. & Med.* **47**:525, 1941.

The gastric mucin was fed to the 8 birds in group S-1-7 in table 1 with the expectation that this extract of gastric secretion might prove protective against gastric ulceration in chicks, as such protection has been claimed in treating peptic ulcers in human beings. However, not only did the mucin not prove protective, but the degree of ulceration in group S-1-7 was twice as severe as in the controls. This untoward effect of the mucin might be attributed to its histamine content, but this particular preparation is presumably histamine free. It may have been constipating, causing greater toxicity from the cinchophen, or the mucin itself may have some unknown toxic properties. It should be studied further.

An experiment with a liquid preparation of gastric secretion made from the fresh mucosa of the pig (gastron) proved interesting in a similar manner. Seventy-five grams of mucosa yields 100 cc. of solution, which contains active pepsin and approximately 0.25 per cent hydrochloric acid. It was supplied in the drinking water, with 3.3 cc. (2.5 Gm. fresh mucosa) allowed per bird per day in 2 experiments, but was offered as a substitute for drinking water in group S-2-2. It proved so toxic for this last group that only 2 birds survived the experiment, and no deductions could be drawn. One of the other two groups was used as a control, while 1 per cent cinchophen was fed to the second. The chicks receiving cinchophen showed a grade of ulceration of 1.35, which was three times as severe as that of the control group given gastron without cinchophen but was also more than twice as severe as that of the control groups given cinchophen without gastron. Evidently, the gastron made the birds more vulnerable to cinchophen ulceration, possibly by increasing the amount of peptic activity of the chicks' stomach contents.

#### BILE THERAPY

Four years ago Almquist and Mecchi<sup>16</sup> reported the protective action of bile on gizzard erosions. They found that whole bile, fresh or dried; concentrated beef bile; sodium glycocholate; sodium taurocholate; cholic acid, and dehydrocholic acid were all highly effective when fed as 0.5 per cent of the diet. Desoxycholic acid was not nearly so effective, nor was dehydrocholic acid when given by intramuscular injection. Two years ago I tested the protective activity of two commercial preparations of bile salts comprising 2 per cent of the diet. The first, a combination of sodium glycocholate and sodium taurocholate (Fairchild Brothers and Foster), gave complete protection to all 10 birds fed. The second, iron bile salts (bilron, Lilly), gave almost complete protection.

In a further paper in 1941 Almquist and Mecchi<sup>15</sup> confirmed their previous observations on the effect of bile acids on gizzard erosions due

16. Almquist, H. J.: Influence of Bile Acids on Erosions of the Chick Gizzard Lining, *Science* **87**:538, 1938. Almquist, H. J., and Mecchi, E.: The Influence of Bile on Erosions of the Chick Gizzard Lining, *J. Biol. Chem.* **126**:407, 1938.

to dietary deficiency and noted the same protective action of bile acids and salts against similar lesions produced by feeding cinchophen. They found a marked increase in cholic acid in the gizzard lining and in the gallbladder bile of birds fed cholic acid but not in those fed types of bile acids other than glycocholic acid. Ox bile salts also produced a high cholic acid content of the chick bile. They concluded that the protective action of certain bile acids, particularly cholic acid, and of bile salts against gastric lesions due to a deficient diet or due to cinchophen is dependent primarily on "bile and especially cholic acid coming in periodic direct contact with the lining serving naturally to aid in maintaining the lining in sound condition."

In 1940 I fed 2 per cent of a combination of sodium glycocholate and sodium taurocholate to a group of 8 chicks receiving 1 per cent cinchophen added to a slightly deficient diet (table 1). Characteristic cinchophen ulcers developed in all but 1 of these birds, and the average score was 2.5. This score was not significantly less than that for the control group, which did not receive cinchophen. It was 2.67. In two subsequent experiments, shown in table 1, 2 per cent cholic acid was added to a protective diet which had given an ulcer score of 0.25. In the first experiment 0.5 per cent cinchophen was also added to the diet and in the second 1 per cent cinchophen. In the first, a lesion developed in only 1 of 6 birds, giving an average score of only 0.33, but the control series of 10 birds for this group, which did not receive cholic acid, had an average score of only 0.15. Similarly, of the 6 birds in the second experiment, lesions developed in 2, giving an average score of 0.92, but the control group had an average score of only 0.61. These experiments with bile salts and cholic acid do not show evidence of any protection against cinchophen gastric ulcers, and this negative result is in accord with a similar one already reported.<sup>2</sup>

These results are just the opposite from those of Aimquist and Mecchi, but it should be noted that they used a different method of grading the gastric lesions. Their method is based on the extent of surface involvement and not on the depth of the ulceration. Many penetrating and perforating ulcers occur singly and may be not over 1 to 2 mm. in diameter. This type of lesion would tend to give a low score by their method and a high one by my method. The two cannot justly be compared.

#### OTHER EFFECTS OF CINCHOPHEN

Cinchophen feeding markedly affects the general nutrition of the bird. The early toxic effects tend to abate somewhat after the second or third day, presumably because the birds eat less per day. One-half per cent of cinchophen produces little or no toxicity, but 1 per cent

cinchophen nearly always affects the birds noticeably. However, in birds taking highly protective diets the signs of toxicity may be completely lacking. This neutralization of the usually encountered toxic signs was complete in the birds receiving 10 per cent dried leaves of cereal grasses cerophyl in the diet and almost complete in the groups receiving 5 per cent dried leaves of cereal grasses, milk and liver. A low grade of gizzard ulceration could be predicted in those birds failing to show signs of toxicity when first offered a diet containing 1 per cent cinchophen.

The birds' appetites were depressed early when fed cinchophen, and this, together with the frequent passage of the characteristic watery mustard-like stools, resulted in slow gain in weight after the first week compared to the control birds which received no cinchophen. If the

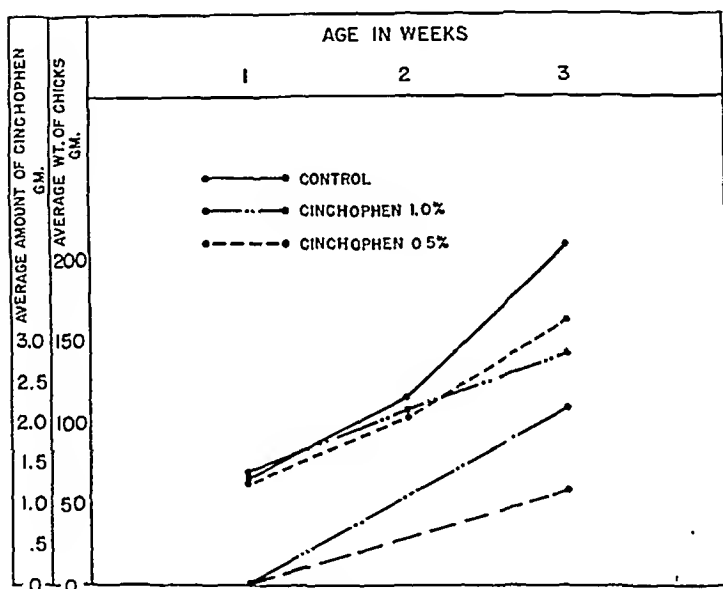


Fig. 7.—The retarding effect of cinchophen fed as 0.5 per cent and as 1 per cent of a vitafood diet on the growth of groups of chicks as shown by a comparison of their average weight curves with that of a normal control group of birds. There were 10 birds in each of the three groups. The lower curves indicate the amount of cinchophen ingested.

chicks were on a deficient diet as well, the retardation in growth was manifest earlier and was more pronounced. The comparative weights at the time of autopsy shown in table 1 show the pronounced variations which may occur with cinchophen therapy and different forms of feed.

The effect of cinchophen on gain in weight is well illustrated in figure 7. Three groups of 10 1 week old chicks were used for this experiment, and all received the highly protective diet vitafood. One group received 0.5 per cent cinchophen in the diet for two weeks; one received 1 per cent cinchophen, and the third served as a control, receiving the diet without cinchophen. The first two groups gained

almost the same amount of weight for the first week, increasing 405 and 388 Gm. respectively, while the control group gained 500 Gm. But by the end of the second week, the group receiving 0.5 per cent cinchophen had gained 600 Gm. more and the group on 1 per cent cinchophen only 360 Gm. more. The control group gained another 930 Gm. for the same period. The amount of cinchophen consumed for the two week period was computed from the amount of diet eaten. All such quantitative determinations are inaccurate in these experiments as an unknown amount of the feed is wasted by the chicks. Nevertheless, the figures of 11.9 and 21.9 Gm. represent a reasonable approximation of the relative amount of cinchophen taken by each of the two groups, based on the first group consuming 2,380 Gm. of feed and the second group 2,190 Gm. The larger amount of cinchophen ingested is clearly associated with a gain in weight in the second week of 40 per cent less than in the other group despite the fact that the dietary consumption was only 8 per cent less for the same period. This indicates that the toxic effect of cinchophen retards growth in some other manner than by depressing appetite and thereby cutting down food consumption. Lehman and Hanzlik<sup>17</sup> came to the same conclusion in 1933 when feeding cinchophen to rats and rabbits.

Possibly an increase in diarrhea may be a factor, as table 1 shows little ulceration occurred in either of these two groups (S-1-1 and S-1-8) despite the lack of satisfactory gain in weight.

No consistent postmortem changes other than ulcers in the gizzard have been found. In a few experiments previously noted<sup>2</sup> gross changes in the liver were observed under special dietary conditions coincident with cinchophen feeding. No histologic evidence of hepatitis or necrosis has been identified, but it should be noted that lethal doses of cinchophen have been avoided and only short time experiments have been carried out. No birds have been treated with this drug longer than one month and most of them for less than two weeks. Further studies of the effects of cinchophen on the liver will be reported at a later date.

#### THE NATURE OF THE DISORDER

The cause of erosions developing in the lining of the gizzard of chicks fed on a deficient diet is perfectly clear. The birds' food must contain an "anti-gizzard erosion factor," or lining lesions will occur, and an ample supply of this factor in the feed will prevent or clear up lesions. The factor has to do with the normal nutrition of the gastric mucosa in the muscular portion of the stomach. If it is inadequate in amount, mucosal bleeding takes place which may lead to ulceration. As

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17. Lehman, A. J., and Hanzlik, P. J.: Cinchophen Toxicosis, *Arch. Int. Med.* 52:471 (Sept.) 1933.

the earlier pathologic manifestations of the deficiency are identical with those occurring in birds fed cinchophen and as they may be prevented or cleared up by feeding the same dietary factor, it seems evident that the basic nature of the lesions attributed to cinchophen and those due to a deficient diet will be the same. If this toxic drug interferes with the assimilation of the dietary factor, the gastric mucosa will be deprived of the necessary protective substance just as if it were barred from the diet. There is an excellent precedent for this explanation in two well recognized types of vitamin K deficiency. The diet may be deficient in vitamin K, causing prolonged blood and plasma coagulation times, or severe hepatic damage despite an adequate diet may interfere with the metabolism of vitamin K and cause the same end result—tendency to a fatal hemorrhage.

The possibility of cinchophen causing a toxic effect on the gizzard lining by direct contact must be considered, but this hypothesis does not seem probable for three reasons: First, the initial lesion, bleeding, is beneath the chitinous lining of the gizzard and not at the surface. Second, the early erosive lesion does not develop until one or more days after cinchophen has been introduced. If the drug action was a direct toxic one, lesions should appear earlier. Third, it has been demonstrated in dogs that cinchophen gastric ulcers can be produced by injecting the drug intravenously when no direct contact with the gastric mucosa ever occurs.<sup>18</sup> While administration by this route has not yet been tried in chicks, it is logical to assume that if cinchophen gastric ulcers in dogs (and cats) are produced indirectly, the same mechanism would be applicable to birds. In order to test this hypothesis, 7 birds 3 months old weighing approximately 1 Kg. each were given intraperitoneal injections daily for ten days of a solution of cinchophen containing 0.02 Gm. per cubic centimeter. The conditions and results of this experiment are recorded in table 2. Five of the birds so treated showed definite lesions, with an average ulcer score for the whole group of 1.36. The 5 control birds on the same diets but not receiving cinchophen did not show lesions in the gizzard, giving an ulcer score of 0. Although the groups of birds studied are small, the development of lesions in 71.4 per cent of those receiving cinchophen parenterally contrasted to the absence of lesions in the control group is good evidence that cinchophen gastric ulcers can be produced in chickens without introducing the drug into the stomach. Consequently, until positive proof is offered to the contrary, cinchophen gastric ulcers in chicks may be considered as due to some indirect action of the drug.

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18. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen; Methods of Production. The Effect of a Mechanical Irritant and the Life History of the Ulcer, *Arch. Surg.* **35**:290 (Aug.) 1937.

On account of cinchophen's well known capacity for damaging the liver in human beings as well as in experimental animals, the possibility that hepatic damage may be the indirect cause for gastric ulceration in chicks must be explored. The lack of positive histologic evidence for this does not settle this point, as it is readily conceivable that a disorder in hepatic function can occur without morphologic evidence. The beneficial effect of feeding hog liver fat and fresh liver shows that at least liver contains the antiulcer factor, and evidence is presented in table 1 that feeding cinchophen to an animal may destroy this factor. Further support to this theory is offered by a group of birds now under observation which are receiving 5 per cent diethylene dioxide (dioxane) in the drinking water. This substance has a selective toxic action on the

TABLE 2.—*Ulceration in Gizzards of Chicks Following Parenteral Administration of Cinchophen\**

Bird No.	Diet	Amount of Cinchophen	Ulcer Score	Comment
1	Vitafood	5 cc. (0.1 Gm.)	1.5	1 lesion
2	Vitafood	5 cc. (0.1 Gm.)	2.0	2 large lesions
3	Vitafood	5 cc. (0.1 Gm.)	0	Normal
4	Vitafood	None	0	Control, no lesions
5	Vitafood	None	0	Control, no lesions
6	Basal diet	10 cc. (0.2 Gm.)	2.0	3 lesions
7	Basal diet	10 cc. (0.2 Gm.)	1.5	2 small lesions
8	Basal diet	5 cc. (0.1 Gm.)	0	Normal
9	Basal diet	5 cc. (0.1 Gm.)	2.5	3 large lesions
10	Basal diet	None	0	Control, no lesions
11	Basal diet	None	0	Control, no lesions
12	Basal diet	None	0	Control, no lesions

\* Each of 7 birds weighing approximately 1 Kg. received ten daily intraperitoneal injections of a solution of cinchophen. Lesions developed in 5. Five control birds did not show any lesions in the gizzard.

liver and kidney.<sup>19</sup> Nine birds were killed between the eighth and the twelfth day of the experiment. All 9 showed gastric ulcerations of the same type as develop when cinchophen is fed. This experiment will be reported on in detail at a latter date. At present it would seem justifiable to assume that cinchophen alters hepatic function and thereby interferes with the normal delivery of the protective substance to the gastric mucosa.

Such a hypothesis would be consistent with the present state of knowledge concerning the administration of bile salts and bile acids. They offer excellent protection against lesions due to dietary deficiency, presumably because they facilitate the absorption of the fat-soluble antierosion factor. They may under certain conditions prove similarly effective against cinchophen gastric ulcers for the same reason, but

19. Fairley, A.; Linton, E. C., and Ford-Moore, A. H.: The Toxicity to Animals of 1-4 Dioxan, J. Hyg. 34:486, 1934.

if hepatic function is markedly deranged, they may prove ineffectual, as the factor could not be properly utilized, even though it was absorbed in sufficient amount.

Whatever the *modus operandi* of this fat-soluble antierosion factor, it would seem desirable for the sake of convenience, both for brevity and specificity, to designate it as a vitamin and in view of its antiulcer properties to call it vitamin U. Its characteristics are now so well recognized in experiments on chicks that such terminology would appear to be entirely justifiable.

#### THE PEPTIC ULCER PROBLEM IN HUMAN BEINGS

The gastric ulcers in chicks which have been described as due to a dietary deficiency or to the ingestion of cinchophen or to a combination of both present striking similarities to the peptic ulcers occurring so commonly in human beings. However, there is at present absolutely no positive evidence that the mechanism of production of ulcers in the gizzards of birds is related to the problems of the etiology of peptic ulcers in human beings. Nevertheless, certain similarities cannot be overlooked as offering a new type of evidence that a conditioned nutritional deficiency may be a factor in precipitating the primary lesion in the development of peptic ulcers in patients.

At present it will suffice to point out that ulcers in chicks are always in the muscular part of the stomach where highly acid gastric juice rich in pepsin first strikes the wall and that macroscopically and microscopically they have the characteristics of peptic ulcers developing in animals or man. Similarly, gastric ulcers have been described in dogs, cats<sup>20</sup> and even human beings<sup>21</sup> after the administration of cinchophen. Also the clinical evidence of peptic ulcer varies in certain groups of people or in nations related to the type of diet consumed,<sup>22</sup> and Fanley and Ivy<sup>23</sup> have shown that a special diet can reduce the incidence and modify the severity of experimentally produced jejunal ulcers in dogs.

20. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning in Dogs, *Arch. Path.* **14**: 860-869 (Dec.) 1932. Schwartz, S. O., and Simonds, J. P.: Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog, *Proc. Soc. Exper. Biol. & Med.* **32**:1133-1134, 1935. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Produced by Cinchophen, *Arch. Path.* **26**:44 (July) 1938. Stalker, Bollman and Mann.<sup>18</sup>

21. Reah, T. G.: Cinchophen Poisoning, *Lancet* **2**:504, 1932. Bloch, L., and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning, *Am. J. Digest. Dis. & Nutrition* **1**:29, 1934.

22. Alsted, G.: Studies of the Changing Incidence of Peptic Ulcer of the Stomach and Duodenum, London, Oxford University Press, 1939, p. 20.

23. Fanley, G. B., and Ivy, A. C.: The Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy, *Surg., Gynec. & Obst.* **63**:717, 1936.



The initial lesion in chicks is bleeding, which corresponds to recent gastroscopic observations on human subjects,<sup>24</sup> and the development of the ulcer may be furthered by increasing the hydrochloric acid and pepsin concentration in the gastric contents as shown by feeding gastron. The beneficial effect of milk on gastric ulcers in birds has a well known counterpart in patients with ulcer. The experiments on birds suggest a vitamin factor as responsible for the therapeutic efficacy of milk rather than its liquid form and show that this factor is destroyed by heat.

There is considerable evidence that a disturbance in hepatic function can be responsible for the development of peptic ulcers in chicks. Such a disturbance has also been held responsible for the appearance of ulcers in the stomachs of dogs fed cinchophen,<sup>25</sup> and it has been suggested that there is a clinical relation between altered hepatic function and peptic ulcers in patients.<sup>26</sup> Whether such comparisons between the erosive and ulcerative lesions of birds' gizzards and peptic ulcer in human beings may prove entirely illusionary must depend on the results of future investigations, but the marked similarities between the peptic ulcers of birds and of patients suggest a relation which must be disproved by experimentation before it can be disregarded.

#### SUMMARY

1. It has been demonstrated repeatedly in the last five years that superficial ulcers (erosions) develop in the gizzards of chicks which are fed on a deficient diet. The deficiency is due to the lack of a specific substance termed the anti-gizzard-erosion factor and can be prevented or cured by the addition of this factor to the diet.

2. This factor is fat-soluble, is contained in the sterol fraction of fat which is saponifiable and is readily destroyed by heat. It occurs in close association with, but is definitely separate from, vitamin K and is present in alfalfa, many cereals, liver, fish oils, fresh milk and a variety of other substances.

3. The same type of lesion can be produced in the muscular portion of the chick's stomach by the administration of cinchophen either orally

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24. Schindler, R.: Chronic Localized Gastric Purpura, *Am. J. Digest. Dis.* 5:796, 1939.

25. Reymont, A.: A Study of Liver Function in Experimental Peptic Ulcer, *Am. J. Digest. Dis.* 1:65, 1940.

26. Vilardell, J., and Corachán Lloret, M.: Estudio histológico del hígado (por biopsia) en las colecistitis y ulcus gastro-duodenal, *Rev. méd. de Barcelona* 17:225, 1932. Jergesen, F. H., and Simonds, J. P.: The Blood Lipase in Patients with Peptic Ulcer, *J. Lab. & Clin. Med.* 19:1054, 1934. Schnitker, M. A., and Hass, G. M.: A Histological Study of the Liver in Patients Affected with Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* 1:537, 1934.

or parenterally, and increased amounts of this toxic drug will produce more pronounced and even penetrating and perforating ulcers. These ulcers tend to heal rapidly when cinchophen feeding is stopped.

4. Cinchophen gastric ulcers in chicks are more pronounced the more deficient the diet and grossly and histologically resemble peptic ulcers in human beings. Only acute and subacute lesions have been studied to date.

5. As the same dietary factor evidently prevents or modifies gastric ulcers due to cinchophen that prevents dietary deficiency ulcers, it is suggested that this factor be designated as vitamin U because of its proved antiulcer properties in the chick.

6. Certain bile acids and bile salts will prevent the development of deficiency ulcers in chicks and may have a similar beneficial effect on cinchophen gastric ulcers. This observation is best explained by assuming that bile promotes the intestinal absorption of the fat-soluble factor.

7. It seems probable that the ulcer-producing properties of cinchophen are due not to direct action on the lining of the stomach but to an indirect effect on the liver. Damage to the liver may then interfere with the elaboration and storage of the antiulcer factor and its delivery to the stomach wall. There are a number of independent observations in the literature on ulcers in dogs and in patients to support such a hypothesis.

8. There is at present no proved relation between this antiulcer factor and the problem of the etiology of peptic ulcer in human beings. There is, however, much to justify a critical survey of the clinical problem before dismissing the possibility of such a relation.

# TREATMENT OF PNEUMONIA WITH SULFATHIAZOLE

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AND

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DETROIT

Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) has been widely used for the treatment of pneumococcic pneumonia during the past two years. There are numerous reports attesting to its value, but only one series<sup>1</sup> exceeding 250 cases has been described to date. The following report is based on 557 cases of pneumonia in which treatment was with sulfathiazole.

## METHOD

*Diagnosis.*—The cases included in this study represent all patients over 12 years of age with pneumonia who were admitted to the pneumonia services of the City of Detroit Receiving Hospital and the William J. Seymour Hospital, Eloise, Mich., between Jan. 1, 1940 and Aug. 1, 1941 and who were treated with sulfathiazole. The diagnosis was confirmed by roentgenogram in every case. On admission sputum was typed directly by the Neufeld method, and the results were checked either by mouse inoculation or by the direct typing of a second specimen. Typing was repeated in the event of an extension. Blood cultures were made on admission and were repeated daily. Hemoglobin estimations, white cell counts and differential counts were made frequently during therapy. Red cell counts were made routinely at the beginning and at the end of treatment.

*Dose of Sulfathiazole.*<sup>2</sup>—The dose administered depended on the severity of illness. In the vast majority of cases (420) an initial dose of 60 grains (4 Gm.) was given by mouth and followed by 15 grains (1 Gm.) every four hours around the clock (six times daily) until the temperature remained normal for twenty-four to forty-eight hours. In a limited number of cases (51) doses one-half as large as those just mentioned were given. In 71 cases in which the patients were critically ill an initial dose of 60 grains (4 Gm.) of sodium sulfathiazole was given intravenously. In most instances this dose was repeated two hours later. Thereafter, in these cases the patients received sulfathiazole orally or the sodium salt intravenously in doses of 15-30 grains (1-2 Gm.) every four hours until convalescence was established. Type-specific antipneumococcus serum was given as a supplement in 23 cases in which the patients were critically ill and in which the causative pneumococci were distributed by type as follows: type I, 5 cases;

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From the Department of Medicine, Wayne University College of Medicine.

1. Schwartz, L., and Flippin, H. F.: Sulfathiazole in the Treatment of Pneumonia, *Pennsylvania M. J.* 44:446, 1941.

2. Most of the sulfathiazole used in this study was furnished by E. R. Squibb and Sons and Merck and Company.

TABLE 1.—Summary of Pertinent Data in Five Hundred and Fifty-Seven Cases of Pneumonia in Which Treatment Was with Sulfathiazole

Type of Causative Pneumococcus	Age, Yr.							Duration of Therapy, Hr.		Consolidation			Blood Culture Colony Count			White Cell Count Below 6,000 per Cu. Mm.	Total No. of Cases Deaths
	Age, Yr.							Duration of Therapy, Hr.		Consolidation			Blood Culture Colony Count				
	10-19	20-29	30-39	40-49	50-59	60-69	70+	<96	>96	Lobar Pneumonia	Bron- cho- pneu- monia	N. D.*	<10	10-100	100+		
I.....	1	14(1)†	19	11	8(2)	6(2)	2(1)	33(2)	24(3)	44(4)	14(2)	3	3(1)	2	1	0	
II.....	2	1	8(1)	6	10(2)	2	1(1)	22(2)	7(1)	18(1)	13(3)	2	1	5(1)	3(2)	4(1)	
III.....	3	3	6	8(2)	8(3)	7(4)	7(2)	21(4)	14(4)	21(6)	11(6)	7	0	3(1)	4(4)	33	
IV.....	5	7(1)	6(1)	10	9(1)	6	2	26(1)	10(1)	21	15(3)	9	3	4	0	45	
V.....	1	5	5	2(1)	2	1	2(1)	10(1)	8(1)	10	7(1)	1(1)	1	3	2(1)	18	
VI.....	1	1	3(2)	2	3(1)	3	4	11	5(2)	7	3(2)	7(1)	0	1(1)	1(1)	17	
VII.....	8	7	9(2)	8(1)	4(1)	1	0	24(1)	10(2)	17(2)	17(2)	3	5	3	3(2)	4	
VIII.....	2	5	3	5(2)	9(1)	3(1)	4(1)	23(3)	5(2)	17(1)	4(2)	10(2)	1	3(1)	1(1)	37	
IX.....	0	0	3	1	3	2	0	6	2	4	3	2	0	0	0	31	
X.....	0	1	3	2	4	1	1	6	4	7	2	3	2	1	0	9	
XI.....	1	0	2	0	1	2	1(1)	0(1)	2(1)	4	0	3(1)	0	0	0	12	
XII.....	0	2	2(1)	1	2	0	1(1)	5(1)	2(1)	5	1(1)	2(1)	1(1)	0	0	7	
XIII.....	0	1	4	2	1	3	0	5	4	8	0	3	0	0	0	8	
XIV.....	0	0	1	1	1	1	0	2	0	3	0	0	0	0	0	11	
XV.....	0	0	1	4(1)	0	0	0	4	2(1)	1	1(1)	0	0	0	0	3	
XVI.....	1	1	1	2	2(1)	1	0	3	3	5	1	4	0	0	0	6	
XVII.....	0	2	4	1	3	0	1	6	3	4	2	5	0	0	0	8	
XVIII.....	3	3	4	3	0	0	2(1)	9(1)	2	6	3	6(1)	0	0	0	11	
XIX.....	1	1	3	2(1)	5	1	0	8	4(1)	10	1	2(1)	0	1	0	15	
XX.....	1	2	4(1)	3	4	3	0	12(1)	1	9	2	0(1)	0	0	0	13	
XXI.....	1	1	1	2	1	2	0	2	3	4	0	0	0	0	0	17	
XXII.....	1	1	2	2	1	0	0	5	1	4	0	3	0	0	0	8	
XXIII.....	0	0	1	2	3	1	0	3	1	3	3	1	1	0	0	7	
XXIV.....	0	0	0	0	2	1	2	3	0	2	2	0	2(1)	1	0	0	
XXV.....	0	0	0	0	4(2)	0	1(1)	2(1)	4(1)	2	5(3)	0	0	0	2(2)	5	
XXVI.....	0	0	0	1	0	0	0	1	0	1	1	0	0	0	0	1	
XXVII.....	0	0	0	1	0	0	1(1)	0	0	0	1	0	0	0	0	1	
XXVIII.....	0	0	0	3	2	2	1	10(1)	0	4(1)	1	3(1)	0	0	0	7	
XXIX.....	1	0	2(1)	3	2	2	1	2(1)	1	1(1)	2	5	0	0	0	4	
XXX.....	0	0	0	2(1)	0	0	0	3	3	4	3	0	0	0	0	11	
XXXI.....	1	1	1	2	0	2	0	6(1)	1(1)	6(1)	1(1)	0	1(1)	0	0	7	
XXXII.....	1	1	1	2	0	2	0	3	3	4	3	0	1	0	0	3	
XXXIII.....	1	3	2(1)	0	0	1(1)	0	6(1)	1(1)	6(1)	1(1)	0	1(1)	0	0	7	
No pneumococci.....	8	19(1)	15(1)	15(1)	12(1)	6(2)	15(4)	45(3)	12(2)	38(1)	8(3)	37(5)	0	0	0	83	
Pneumococcus not typable....	0	1	1	1	0	0	0	1	0	1	0	2	0	0	0	3	
Total.....	44	76	120	104	106	53	49	325	135	291	129	137	22	42	17	557	
		(2)	(11)	(10)	(15)	(10)	(15)	(25)	(23)	(17)	(30)	(16)	(4)	(7)	(13)	(11)	

\* N. D., blood culture positive for pneumococci; colony count not done.  
† The figure in parentheses indicates the number of deaths.

type II, 6 cases; type III, 5 cases; type IV, 2 cases; type V, 1 case, and type VII, 4 cases. During the early part of the study an equal amount of sodium bicarbonate was given with each dose of sulfathiazole. Since this was found inadequate for alkalinization of the urine, the dose was later increased to one teaspoonful. The level of sulfathiazole in the blood was determined within twenty-four hours of the beginning of medication and daily thereafter.

#### SUMMARY OF CASES

*Age, Sex and Race.*—The age distribution is given by decade in table 1. In more than one half of the cases (57 per cent) the patients were over 40 years of age. The proportion of males was 78 per cent. The race distribution was as follows: white patients, 63 per cent, Negro patients, 37 per cent.

*Type and Severity of Pneumonia.*—Most of the significant data are summarized in table 1. The interval between the onset of pneumonia and the beginning of chemotherapy exceeded ninety-six hours in 29 per cent of the cases. The pneumonia was classified as lobar in 75 per cent of the cases. More than one lobe was involved in 31 per cent of this group. Pneumococcic bacteremia was present in 19.4 per cent of cases of pneumococcic pneumonia (16.3 per cent of the entire series). Colony counts were done in 60 cases of bacteremia, and over 100 organisms per cubic centimeter were found in 28 per cent. The leukocyte count on admission was below 6,000 in 35 cases (6 per cent) and was between 6,000 and 10,000 in 78 additional cases (14 per cent).

*Associated Diseases.*—A history of daily consumption of large amounts of alcohol was obtained in 97 cases (17 per cent), in many of which the patients were admitted in delirium tremens. In a total of 38 cases there was definite clinical evidence of congestive heart failure; in 36 others there was compensated organic heart disease. Cirrhosis was encountered in 8 cases; toxic hepatitis was present on admission in 3 others, and moderate to marked azotemia was present before therapy in a total of 18 cases. There were 6 cases of diabetes mellitus, 9 cases of a malignant growth, 9 cases of chronic pulmonary tuberculosis and 21 cases of chronic asthmatic bronchitis or bronchiectasis. Empyema was present on admission in 5 instances. The pneumonia was secondary to chest injury in 12 cases and followed operation in 36.

#### RESULTS

*Fatality Rate.*—The uncorrected fatality rate for the entire series of 557 cases was 11.3 per cent. The fatality rate by decade was as follows: second decade, 0; third, 2.6 per cent; fourth, 9.1 per cent; fifth, 9.6 per cent; sixth, 14.1 per cent; seventh, 17.2 per cent, and eighth and over, 30.6 per cent. In those cases in which treatment with sulfathiazole was started within ninety-six hours of the onset of pneumonia the fatality rate

was 7.6 per cent; in the remainder it was 17.0 per cent. There were 5.8 per cent deaths in the cases of lobar consolidation confined to one lobe, 23.2 per cent deaths in cases of consolidation of two or more lobes and 11.6 per cent deaths in cases of bronchopneumonia. The fatality rate for all 92 cases of bacteremia was 28.2 per cent. A breakdown of these figures according to colony count gave the following results: less than 10 organisms per cubic centimeter, 16.6 per cent deaths; 10 to 100 per cubic centimeter, 18.2 per cent deaths, and over 100 per cubic centimeter, 76.4 per cent deaths.

*Analysis of Deaths.*—An analysis of the deaths is presented in table 2. In 19 cases death occurred within twenty-four hours of the institution of sulfathiazole therapy. If these cases were excluded, the corrected fatality rate would be 8.1 per cent. In 24 additional cases the patients were considered to have terminal pneumonia complicating serious debilitating disease (such as cardiac failure or uremia). If these were also excluded, the corrected fatality rate would be 3.9 per cent. In 3 cases death was due to empyema or abscess of the lung, and in 3 it was due to pneumococcic endocarditis. In at least 1 of the latter the endocarditis was probably present on admission. In 5 cases fatal extension developed after apparent response to chemotherapy. In 1 case (60) an extension of the patient's pneumonia caused by pneumococci of type I and a blood culture positive for these organisms developed during the administration of sulfathiazole. The organisms recovered from the blood stream were resistant to sulfathiazole in vitro, growing in mediums containing 20 mg. per hundred cubic centimeters. In 1 case death from circulatory collapse followed the administration of epinephrine. Toxic reactions from sulfathiazole were a major factor in death in 2 cases. In 1 of these cases (61) the patient died in anuria after exfoliative dermatitis. In the other case (63) the patient showed numerous acetyl-sulfathiazole calculi in both kidneys at autopsy.

*Clinical Effects.*—The temperature fell to normal within twenty-four hours of the institution of sulfathiazole therapy in 145 cases (26 per cent) and within forty-eight hours in a total of 288 cases (51.7 per cent). The concentration of free sulfathiazole in the blood was determined at defervescence in 299 cases. It was below 2 mg. per hundred cubic centimeters in 83 cases, between 2 and 4 mg. in 124 cases, between 4 and 6 mg. in 59 cases and over 6 mg. in 33 cases. The temperature fell by crisis in many cases in which the blood levels of sulfathiazole consistently were between 1.5 and 3 mg. per hundred cubic centimeters. The blood culture became negative for pneumococci in 76 of the 92 cases of bacteremia (82.6 per cent). In most instances this occurred within twelve to twenty-four hours of the institution of chemotherapy. In 10 cases in which the blood culture became negative the patients died sub-

TABLE 2.—Analysis of Deaths

Case No.	Type of Pneumococcus	Age, Yr.	Blood Culture, Colonies per Cc.	No. of Lobes Involved	White Cells per Cc.	Duration of Therapy	Total Dose, Grains	Serum, Units	Overwhelming Infection, Death Within 24 Hours	Comment
1	I	90	1	2	.....	11 hr.	150	.....	Aged 90	
2	II	59	6	3	6,300	17 hr.	150	600,000	Postoperative perforated peptic ulcer	
3	II	53	5,000	3	3,100	10 hr.	120	180,000	Delirium tremens on admission; peripheral circulatory collapse; autopsy showed toxic myocarditis	
4	II	33	1,900	3	6,100	16 hr.	180	200,000	Arteriosclerotic heart disease	
5	III	68	5,000	2	10,200	9 hr.	135	.....	Delirium tremens and empyema on admission	
6	III	49	0	2	2,900	9 hr.	120	100,000	Delirium tremens; extreme leukopenia	
7	III	49	600	1	1,000	9 hr.	150	170,000		
8	III	52	0	2	7,000	20 hr.	180	100,000		
9	III	56	780	1	14,200	5 hr.	120	80,000		
10	III	67	1	2	15,000	11 hr.	240	360,000	Autopsy: coronary sclerosis with old myocardial infarct; death from pneumonia	
11	VI	37	6	2	9,400	7 hr.	90	.....	Delirium tremens, hepatitis (icterus index 115); in circulatory collapse on admission	
12	VII	50	6,000	3	5,600	9 hr.	165	280,000	Delirium tremens	
13	VII	39	0	1	15,400	18 hr.	120	.....		
14	VII	41	7,000	4	2,700	7 hr.	150	200,000		
15	VIII	47	1,900	2	1,300	8 hr.	120	.....	Delirium tremens	
16	XXV	61	5,000	3	2,400	18 hr.	240	.....		
17	XXXIII	38	40	3	2,200	15 hr.	195	.....	Blood culture sterilized before death	
18	III	61	180	3	3,500	25 hr.	165	.....	Overwhelming Infection, Death Within 48 Hours	
19	IV	57	0	3	3,300	24 hr.	270	100,000	Blood culture sterilized before death	
20	IV	27	25	4	6,300	39 hr.	225	300,000	Delivery (full term) in hospital; empyema on admission	
21	V	46	183	4	28,200	48 hr.	315	100,000	Delirium tremens; blood culture sterilized before death	
22	I	62	0	1	10,400	19 hr.	60	.....	Terminal Pneumonia, with Serious Associated Disease	
23	I	56	0	1	22,500	14 hr.	120	.....	Right bundle branch block, cirrhosis; death 19 hr. after sulfathiazole started, but dosage inadequate	
24	I	61	0	1	28,400	3.5 days	220	.....	Delirium tremens; cardiac failure	
25	II	80	0	1	14,300	1.5 days	195	.....	Cardiac failure and uremia (blood urea 312 mg./100 cc.); temperature normal for 3 days before death; no autopsy	
26	III	67	0	1	12,500	6 days	465	.....	Hypertension with cardiac failure	
27	III	72	0	1	10,400	6 days	510	.....	Cocurrent most arteriosclerotic gangrene of leg	
28	V	70	0	1	11,000	19 days	1,245	.....	Cardiac failure; temperature normal for 6 days before death; clinical impression was that pneumonia had cleared up; no autopsy	
29	VIII	73	0	2	23,400	3.5 days	375	.....	Failure of right side of heart; temperature normal for 5 days before death; no autopsy	
30	VIII	40	0	3	13,000	3 days	285	.....	Death; no autopsy	
31	VIII	61	0	2	22,700	5 days	540	.....	Comatose and in circulatory collapse on admission; autopsy showed coronary sclerosis, myocardial fibrosis, acute myocarditis and acute fibrinous pericarditis	
32	XI	72	0	2	10,600	5 days	625	.....	Delirium tremens throughout stay in hospital	
33	XII	30	0	2	19,700	4 days	615	.....	Blood urea 164 mg./100 cc. on admission; aortic insufficiency; chronic asthmatic bronchitis	
34	XV	47	0	2	21,800	13 days	975	.....	Delirium tremens with left ventricular failure; no therapeutic response	
35	XVI	60	0	1	12,200	2 days	200	.....	In circulatory collapse on admission; autopsy revealed severe chronic pycelonephritis, cardiac hypertrophy and secondary pneumonia caused by hemolytic streptococcus	
36	XIX	40	0	1	19,100	25 hr.	120	.....	Lumpectomy for epidural abscess; chronic pycelonephritis	
37	XX	39	1	3	32,400	2 days	170	.....	Korsakoff's psychosis	
38	XXVIII	71	0	1	13,700	3 days	405	.....	Six months' pregnancy; mild pneumonia with favorable progress until advent of spontaneous abortion; circulatory collapse during delivery; death shortly afterward	
39	XXXI	18	1	1	13,000	1 day	175	.....	Acute glomerulonephritis with uremia, hypertensive encephalopathy and terminal left ventricular failure; blood culture sterilized; death from nephritis	
									Hyperpension with cardiac failure	
									Portal cirrhosis; blood culture negative before death	

40	XXXIII	66	+	1	15,600	12 days	1,050	.....	Arteriosclerotic heart disease with failure
41	No pneumo- coccus	65	0	3	21,000	0 days	800	.....	Hypertension with cardiac failure
42	No pneumo- coccus	76	0	2	35,700	7 days	705	.....	Fracture of neck of femur; arteriosclerotic heart disease with failure
43	No pneumo- coccus	73	0	2	10,500	7 days	660	.....	Chronic pulmonary tuberculosis; arteriosclerotic heart disease; bronchietasis
44	No pneumo- coccus	18	0	2	4,300	5 days	465	.....	Delirium tremens; extreme dyspnea and cyanosis disproportionate to pulmonary signs and suggestive of pulmonary embolism; no autopsy
45	No pneumo- coccus	70	0	2	16,900	9 days	690	.....	Fracture of tibia and fibula; arteriosclerotic heart disease with failure
46	No pneumo- coccus	60	0	1	15,500	1.5 days	165	.....	Delirium tremens; congestive heart failure
47	No pneumo- coccus	56	0	2	20,500	1.5 days	165	.....	Cerebral hemorrhage with hemiplegia
Death from Complications of Pneumonia									
48	III	59	0	2	12,100	6 days	510	.....	Abscess of lung and empyema; death after operation
49	VI	52	102	2	9,100	4 days	555	.....	Autopsy showed vegetative endocarditis caused by pneumococci of type VI superimposed on rheumatic aortic stenosis
50	VI	36	0	3	4,900	9 days	840	.....	Chronic alcoholism; admitted in barbitic coma; empyema developed; death from cellulitis caused by hemolytic streptococcus
51	VIII	57	1	1	6,900	5 days	495	.....	Chronic alcoholism; admitted in coma; blood culture sterilized; autopsy showed multiple abscesses of lung
52	XXV	71	+	3	11,500	22 days	2,515	.. ....	Autopsy showed vegetative endocarditis caused by pneumococci of type XXV
53	XXV	59	350	3	14,700	5 days	450	.....	Aortic insufficiency 24 hr. after sulfathiazole started; autopsy showed vegetative endocarditis caused by pneumococci of type XXV
Therapeutic Failure, Death from Extension or Drug Resistance									
54	IV, VI, XVII	36	0	2	17,000	4 days	375	.....	After 3 days' normal temperature extension developed; autopsy showed chronic pyelonephritis, productive pulmonary tuberculosis with terminal pneumonia; no pneumococci in lung at autopsy
55	XVII, VIII, XII	71	0	2	17,900	6 days	510	.....	After 4 days of normal temperature with apparent recovery from original pneumonia, consolidation caused by pneumococci of type XII and bacteremia developed; blood culture sterilized before death
56	XVIII	82	0	2	9,100	8 days	795	.....	After 2 days of normal temperature, extension developed; no pneumococci in sputum; no response to second course of sulfathiazole
57	XXIX	34	0	1	13,500	3 days	300	.....	Lymphatic and splenic tuberculosis; after 2 days of normal temperature with roentgen evidence of resolution of original pneumonia, fever recurred; autopsy revealed diffuse terminal bronchopneumonia
58	No pneumo- coccus	87	0	1	10,900	5 days	510	.....	Terminal pneumonia with temporary response to chemotherapy, then a fatal relapse
59	I	28	+	4	21,300	7 days	675	.....	Extensive pneumonia with marked cyanosis and dyspnea; blood culture sterilized before death from pneumonia
60	I	67	0	1	18,300	4 days	390	.....	Complete therapeutic failure; drug resistant; organisms grew in media containing 20 mg./100 cc. of sulfathiazole; pneumonia extended and blood culture became positive during sulfathiazole therapy; subsequently 720,000 units of antipneumococcus serum and hydroxyethylapocuprine given without clinical effect
Death Due Principally to Reaction to Therapy									
61	III	70	0	1	14,700	6 days	525	.....	Drug fever, conjunctivitis, exfoliative dermatitis and anuria developed; death in uremia; pneumonia completely resolved at autopsy; cirrhosis, nephrosclerosis and cardiac hypertrophy encountered; no calculi or crystals encountered in kidneys, but sulfathiazole considered a major factor in death
62	VII	38	0	1	20,000	36 hr.	180	.....	Underlying asthma; 5 minims (0.31 cc.) of a 1:1,000 solution of epinephrine hydrochloride given; ten minutes later circulatory collapse (blood pressure unobtainable); revival by plasma transfusions, desoxycorticosterone acetate, etc. unsuccessful; autopsy showed marked cerebral hyperemia and small intraventricular hemorrhage
63	No pneumo- coccus	39	0	2	18,400	5 days	555	.....	Chronic osteomyelitis; death in uremia; autopsy revealed many small acetylsulfathiazole calculi in both kidneys, also acute glomerulotubular nephritis thought to be due to sulfathiazole; pneumonia unresolved



sequently. There was clinical and roentgen evidence of extension of the pneumonia during therapy in 35 cases. This included extension within the originally involved lobe as well as spread to other parts of the lung. Resolution was delayed beyond three weeks in 14 cases.

*Complications.*—The incidence of suppurative complications was low. Empyema developed in 6 cases (1 per cent), in all of which surgical therapy was required. There were 2 cases of abscess of the lung, both proved at necropsy. Suppurative arthritis of the shoulder developed in 1 case. The joint continued to drain profusely for one month after surgical incision, at which time direct instillation of sulfathiazole paste was begun. There was a prompt reduction in the amount of discharge,

TABLE 3.—*Toxicity of Sulfathiazole*

Type of reaction	Percentage
Gastrointestinal reaction	
Severe nausea and vomiting.....	1.8
Mild nausea and vomiting.....	9.6
Cerebral reaction	
Severe (delirium or convulsions).....	0.7
Mild (headache, dizziness, drowsiness).....	7.4
Drug fever	
Definite .....	7.6
Questionable .....	2.0
Lesions of the skin and mucous membrane	
Conjunctivitis .....	1.8
Dermatitis (usually papular or nodular).....	3.7
Hematopoietic reaction	
Hemolytic anemia .....	0.2
Fall in hemoglobin exceeding 2 Gm./100 cc. ....	5.9
Leukopenia (3,000-5,000 cells).....	1.8
Reaction in the urinary tract	
Microscopic hematuria .....	9.4
Acetysulfathiazole calculi .....	0.2
Renal insufficiency .....	0.9
Reaction in the liver	
Jaundice .....	0.2

and with supplementary physical therapy a good functional result was obtained. There were 3 cases of fibrinous pericarditis. The diagnosis was based on a characteristic pericardial friction rub and was confirmed at autopsy in 1 instance. In the other 2 cases the patients recovered under sulfathiazole therapy without a clinically recognizable effusion developing. There were 3 cases of acute bacterial endocarditis, all proved at necropsy. In 1 of these cases the patient had terminal pneumococcal meningitis. Secondary bacteremia caused by *Streptococcus haemolyticus* developed in 4 cases, in 3 of which the patients died. In 1 additional case a patient had an associated bacteremia caused by *Staphylococcus aureus* but recovered.

*Toxic Manifestations.*—The incidence of toxic manifestations among the 538 cases in which treatment was with sulfathiazole for a minimum

of twenty-four hours is given in table 3. Nausea and vomiting sufficiently severe to interfere with administration of sulfathiazole were present in only 10 cases. In 1 case a patient had several epileptiform convulsions in association with a blood level of sulfathiazole above 15 mg. per hundred cubic centimeters. After the concentration of this compound in the blood fell below this figure, there were no further convulsions and a complete recovery was made. There were 3 instances of toxic psychosis, in which sulfathiazole was considered a major contributory factor. Mild cerebral symptoms, such as headache, dizziness and drowsiness were recorded in 40 cases. In some instances, however, these symptoms probably resulted from pneumonia rather than from therapy. Drug fever was a fairly common complication in those cases in which sulfathiazole was administered for more than four days. All types of temperature curve were observed. Before we accepted a diagnosis of drug fever, every effort was made to exclude extension and complications of pneumonia. Undoubted drug fever occurred in 7.6 per cent of the cases. Dermatitis developed in approximately one half of the cases of drug fever. The most common varieties were a papular dermatitis involving the hands and face and erythema nodosa-like lesions involving the extremities. Conjunctivitis was present in approximately one fourth of the cases of drug fever. A drop in hemoglobin of more than 2 Gm. per hundred cubic centimeters occurred during the course of therapy in 33 cases. In only 1 of these was the drop of sufficient magnitude and rapidity to warrant the diagnosis of acute hemolytic anemia. In this case, the hemoglobin fell 4 Gm. per hundred cubic centimeters and the red cell count fell 1,100,000 cells per cubic millimeter during the course of six days. The white cell count fell below 5,000 per cubic millimeter during the course of therapy in 10 cases, the lowest count being 2,600 per cubic millimeter. Mild jaundice developed in 1 case during the course of therapy. Microscopic hematuria, exceeding 10 red cells per high power field, occurred in 9.4 per cent of the cases. The hematuria tended to appear when the urine was acid and the output low and to disappear when fluids were forced and the urine was alkalinized. Fatal uremia developed in 2 cases during therapy. In 1 of these (case 61) the patient died in anuria complicating a sulfathiazole exfoliative dermatitis. Autopsy in the other (case 63) revealed many small acetyl-sulfathiazole calculi in both kidneys together with an acute glomerulotubular nephritis, which was thought to be due to the drug. In 3 additional cases renal insufficiency of lesser degree developed.

#### COMMENT

The results of sulfathiazole therapy recorded here were distinctly superior to those previously obtained with sulfanilamide or with sulfa-

pyridine (2-[paraaminobenzenesulfonamido]-pyridine) at the same institutions. The uncorrected fatality rates in cases of roentgenographically proved pneumonia in patients over 12 years of age were as follows: sulfanilamide (369 cases), 23.8 per cent; sulfapyridine (139 cases), 18.7 per cent, and sulfathiazole (557 cases), 11.3 per cent. The corrected fatality rates, excluding deaths occurring within twenty-four hours of the institution of chemotherapy, were 21.1, 18 and 8.1 per cent, respectively. The fatality rates for pneumococcic bacteremia treated with each of the three drugs was as follows: sulfanilamide (73 cases), 48 per cent, sulfapyridine (32 cases), 37.5 per cent, and sulfathiazole (92 cases), 28.2 per cent. A more detailed comparative study, including results of therapy with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) will form the subject of a future communication.

#### SUMMARY

The results of sulfathiazole therapy in 557 cases of pneumonia in adults are presented and analyzed from the standpoint of the type of causative *Pneumococcus*, the age of the patient, the duration of the pneumonia, the extent of the consolidation, the blood culture, the initial white cell count, associated diseases and complications. The uncorrected fatality rate was 11.3 per cent. A tabular analysis of all deaths is included. The incidence of bacteremia was 16.3 per cent, and the fatality rate was 28.2 per cent. Defervescence occurred within forty-eight hours of the institution of sulfathiazole therapy in 51.7 per cent of cases. The incidence of suppurative complications was low. Serious toxic reactions from sulfathiazole were uncommon but were considered a major factor in death in 2 cases. The results of sulfathiazole therapy were superior to those previously obtained with sulfanilamide or with sulfapyridine.

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# MECHANISM OF PENTOTHAL SODIUM ANTIDIURESIS

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Extensive studies of the effects of barbiturates on renal function are few. Epstein investigated the influence of certain barbiturates on diuresis in rabbits caused by thyroxin<sup>1</sup> and by sodium chloride.<sup>2</sup> In 1930 Ogden<sup>3</sup> described the action of amytal in inhibiting water diuresis in dogs during anesthesia, an observation which has been confirmed in many teaching laboratories. Walton<sup>4</sup> and Gouax, Cordill and Eaton<sup>5</sup> did not observe any significant effect of sodium amytal on the twenty-four hour output of urine, though this is rather misleading, since suppression of renal activity during a short period of anesthesia was compensated for by subsequent diuresis. It is, moreover, generally recognized that in clinical cases of severe sodium amytal intoxication secretion of urine is apt to be scanty.<sup>6</sup> In the case of pentothal sodium, it has been reported that when

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This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

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3. Ogden, E.: Inhibition of Water Diuresis by Amytal, *Proc. Soc. Exper. Biol. & Med.* **27**:506-507 (March) 1930.

4. Walton, R. P.: Effect on Kidney Function of Ether, Ethylene, Ethylene and Sodium Isoamyl-Ethyl Barbiturate (Amytal), and Ethylene and Tribromethyl Alcohol (Avertin), *J. Pharmacol. & Exper. Therap.* **47**:141-149 (Feb.) 1933.

5. Gouax, J. L.; Cordill, S. C., and Eaton, A. C.: Influence of Sodium Amytal upon Blood and Urine Urea, *J. Lab. & Clin. Med.* **22**:704-707 (April) 1937.

6. Emge, L. A., and Hoffman, P. E.: Studies on Urinary Excretion in Women Following Administration of Sodium Amytal, *Anesth. & Analg.* **10**:88-90 (March-April) 1931.

the drug was used as an anesthetic in urologic practice, no change in urinary secretion or in the concentration of blood urea occurred.<sup>7</sup>

In this paper the influence of the ultra-short-acting thiobarbiturate pentothal sodium<sup>8</sup> on renal activity has been investigated under a variety of experimental conditions in an attempt to elucidate the mechanism of barbiturate antidiuresis. The experiments described here have been grouped as follows:

1. Effect of pentothal sodium on urine output
2. Antagonism of the demonstrated antidiuretic effect of pentothal sodium by various diuretics
3. Effect of corticosterone acetate and adrenal cortex extract on pentothal sodium antidiuresis
4. Effect of epinephrine on pentothal sodium antidiuresis
5. Effect of solution of posterior pituitary on pentothal sodium antidiuresis
6. Effect of hypophysectomy on pentothal sodium antidiuresis

#### MATERIAL AND METHOD

Male white rats weighing between 160 and 240 Gm. each were employed. All animals fasted for twelve hours before the start of a metabolic period, although they were allowed free access to water during this time. At the end of the preliminary twelve hour fasting period the animals were weighed, given 10 per cent of their body weight of 0.2 per cent sodium chloride solution (warmed to body temperature) by intraperitoneal injection and placed in individual metabolism cages. Urine was collected in 25 cc. graduated cylinders, and the volume recorded at thirty minute intervals during a metabolic period of twelve hours. To insure that no residual urine remained in the bladder, after each interval the bladder was palpated; if urine was present, the fluid was expressed by gentle pressure. In unanesthetized animals this procedure was rarely necessary, but in anesthetized animals with muscular atony it was invariably carefully performed.

All animals to which pentothal sodium was administered were given the calculated dose by intraperitoneal injection at the end of the second hour after fluid was administered. The anesthetic dose for pentothal sodium in these animals, when given by intraperitoneal injection following administration of sodium chloride solution, was found to be 6 mg. per hundred grams of body weight (0.25 cc. of a 2.4 per cent solution). Recovery from this dose was practically complete within six hours, and in several hundred experiments no fatalities resulted. Pratt and associates<sup>9</sup> have given the anesthetic dose of sodium pentothal by intraperitoneal

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7. Tovell, R. M., and Thompson, G. J.: Pentothal-Sodium Anesthesia in Urologic Practice, *J. Urol.* **36**:81-87 (July) 1936.

8. The pentothal sodium was furnished by Dr. J. F. Biehn, of the Abbott Laboratories.

9. Pratt, T. W.; Tatum, A. L.; Hathaway, H. R., and Waters, R. M.: Sodium Ethyl (1-Methyl Butyl) Thiobarbiturate: Preliminary Experimental and Clinical Study, *Am. J. Surg.* **31**:464-466 (March) 1936.

injection as 80 mg. per kilogram of body weight; recovery from this dose took place in six to twelve hours.

Other drugs were employed under special conditions, which will be individually described. These drugs were so administered that they exerted their optimal characteristic action coincident with the antidiuresis produced by the injection of pentothal sodium.

### RESULTS

*Control Diuretic Curve.*—A control diuretic response was established by administering standard water loads to a large series of rats under the controlled conditions just outlined (table 1 A). The diuretic

TABLE 1.—*Effect of Various Doses of Pentothal Sodium on the Urine Output of Rats After Injection of Two-Tenths per Cent Solution of Sodium Chloride\**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	24	2.4	3.5	4.9	5.5	6.0	6.5	7.0	7.5	7.8	8.3	8.6	8.9	9.3	9.5
B (2 mg. of pentothal sodium /100 Gm. of body weight)	12	1.4	1.8	3.3	4.7	5.6	8.3	6.5	7.0	7.5	7.9	8.2	8.5	8.9	9.0
C (4 mg. of pentothal sodium /100 Gm. of body weight)	12	1.9	1.9	2.4	4.8	5.5	6.1	6.7	7.1	7.6	8.0	8.3	8.5	8.8	9.0
D (6 mg. of pentothal sodium /100 Gm. of body weight)	29	2.1	2.3	2.8	3.2	3.6	4.0	4.6	5.2	6.1	6.5	7.2	7.7	8.0	8.3

\* At the beginning of the experiment 10 cc. of saline solution per hundred grams of body weight was injected. When pentothal sodium was used, it was injected at the end of two hours in all experiments.

response to injected fluid under these conditions followed the expected curve (fig. 1), which was easily reproducible in different animals at various times.

Average figures only are given in all tables, beginning with the urine output at the end of two hours. Half hourly readings are recorded until the four and a half hour reading, since these constitute the most significant portion of the curve of diuresis; thereafter, only hourly figures are given in the tables. The graphs represent the best smooth curves which could be drawn through the experimentally determined points.

*Effect of the Injection of Pentothal Sodium on Urine Output.*—Two hours after intraperitoneal injection of sodium chloride solution into several series of rats various doses of pentothal sodium were admin-

istered. When the dose was 2 mg. per hundred grams of body weight the animals became drowsy and disinclined to spontaneous movement, but no anesthesia occurred, and save for a slight diminution in urine flow immediately following the injection, no difference in the diuretic response as compared to that of the control animals was observed (table 1 *B*). When the dose of pentothal sodium was increased to 4 mg. per hundred grams, the degree of hypnosis was more profound and approached light

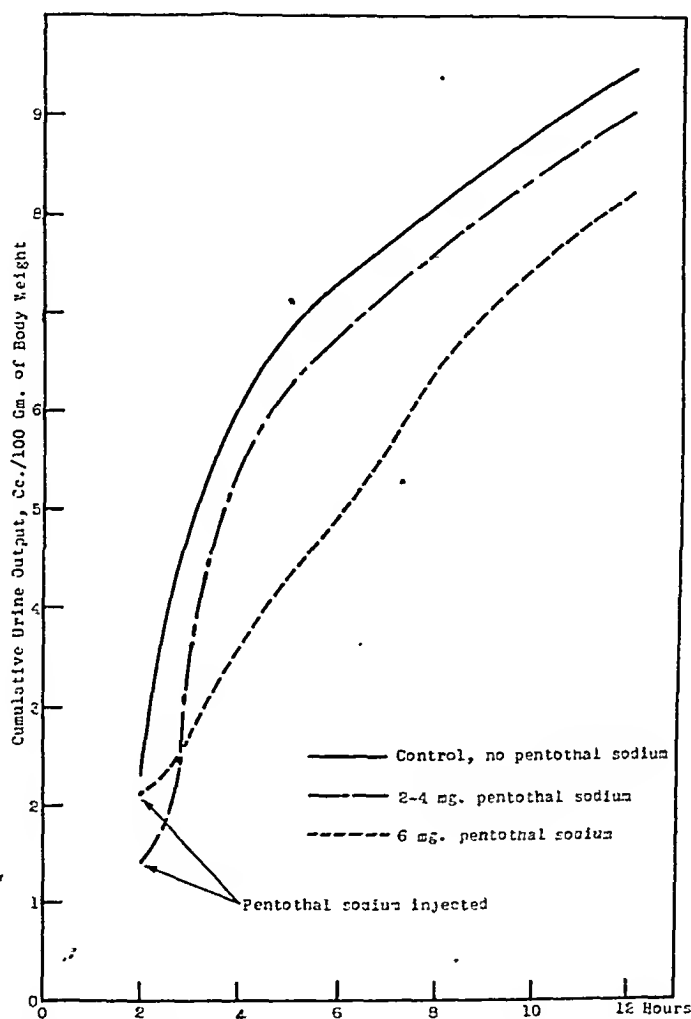


Fig. 1.—Effect of injected pentothal sodium on the urine output of white rats.

anesthesia in about half the animals. The temporary diminution in urine output immediately following injection was somewhat more marked than in the previous series (table 1 *C*; fig. 1).

When the dose was increased to 6 mg. per hundred grams, however, deep anesthesia supervened and lasted for approximately four hours. During this time urine output was markedly decreased, but as the animals recovered consciousness and voluntary movement, the rate of urine flow

once more approached the normal, although the total volume of urine excreted during the twelve hour metabolic period still remained below the control level (table 1 *D*; fig. 1). It should be emphasized here that only fully anesthetic doses of pentothal sodium produced any lasting or significant reduction in the rate and the volume of urine output of rats.

*Influence of Sodium Chloride Solution and Urea on Pentothal Sodium Antidiuresis.*—Two series of animals were given preliminary priming doses of 10 cc. of 0.9 per cent sodium chloride solution per hundred grams of body weight sixteen hours and eight hours before the start of a metabolic period. At the start of the experiment another dose of 0.9 per cent sodium chloride solution was injected in place of the standard dose of 0.2 per cent solution, and the animals were then placed in metabolism cages. Into one of the series of animals pentothal sodium (6 mg. per

TABLE 2.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Nine-Tenths per Cent Sodium Chloride Solution\**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	6	1.8	2.2	3.1	4.2	4.7	5.6	7.3	8.2	8.5	8.8	9.5	9.6	9.7	9.7
B (6 mg. of pentothal sodium /100 Gm. of body weight)	6	2.3	2.3	2.3	2.3	2.6	2.6	3.5	4.8	5.5	6.9	7.2	7.7	8.1	8.6

\* Ten cubic centimeters of saline solution per hundred grams of body weight was injected intraperitoneally sixteen hours and eight hours before and at the beginning of an experiment.

hundred grams) was injected at the end of the second hour. The diuretic response of normal animals to 0.9 per cent sodium chloride solution under these conditions was marked (table 2 *A*), but this diuresis was promptly and severely inhibited by the injection of pentothal sodium (table 2 *B*; fig. 2). It is therefore apparent that large amounts either of water (i. e. hypotonic solution, table 1 *D*) or of sodium chloride (table 2 *B*) acting as diuretics were unable to antagonize the antidiuresis due to pentothal sodium.

A number of experiments were also performed with 1 per cent urea in 0.2 per cent sodium chloride solution used in place of 0.9 per cent sodium chloride solution, with essentially similar (negative) results.

*Influence of Theophylline with Sodium Acetate and with Calcium Salicylate on Pentothal Sodium Antidiuresis.*—Two series of animals were primed with preliminary doses of theophylline with sodium acetate as follows: Twenty-four hours before the start of the experiment each



animal received an intraperitoneal injection of 2 mg. of the drug in solution per hundred grams of body weight. Eight hours and sixteen hours later each animal was given an additional dose of 1 mg. of the drug. On the morning of the metabolism experiment the animals then received intraperitoneal injections of 0.2 per cent sodium chloride solution containing 1 mg. of theophylline with sodium acetate per hundred grams and were placed in the cages as usual. Two hours later one series was given pentothal sodium (6 mg. per hundred grams).

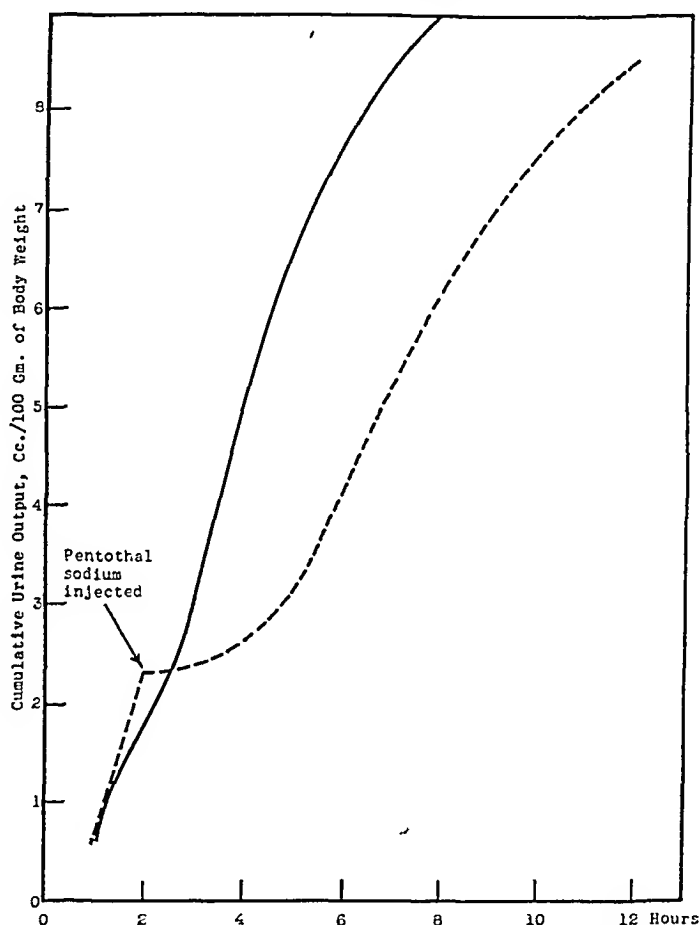


Fig. 2.—Effect of injected pentothal sodium on the urine output of white rats after the administration of 0.9 per cent sodium chloride solution.

The diuretic response of control animals to theophylline with sodium acetate was well marked (table 3 *A*), but this diuretic was nevertheless unable to counteract the pentothal sodium antidiuresis (table 3 *B*). As the anesthetic effect of the barbiturate wore off, however, the diuretic effect of theophylline with sodium acetate became evident; this is well shown by the sudden increase in urine output, corresponding to the emergence of the animals from deep anesthesia (fig. 3).

TABLE 3.—Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Theophylline with Sodium Acetate \*

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	12	4.7	6.1	6.5	6.5	6.7	7.0	7.4	7.9	8.1	8.3	8.6	8.7	8.8	8.8
B (6 mg. of pentothal sodium /100 Gm. of body weight)	12	3.3	3.3	3.5	3.9	4.2	4.7	4.9	5.1	5.4	6.2	6.3	6.8	7.0	7.1

\* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. For the doses of theophylline with sodium acetate, see the text.

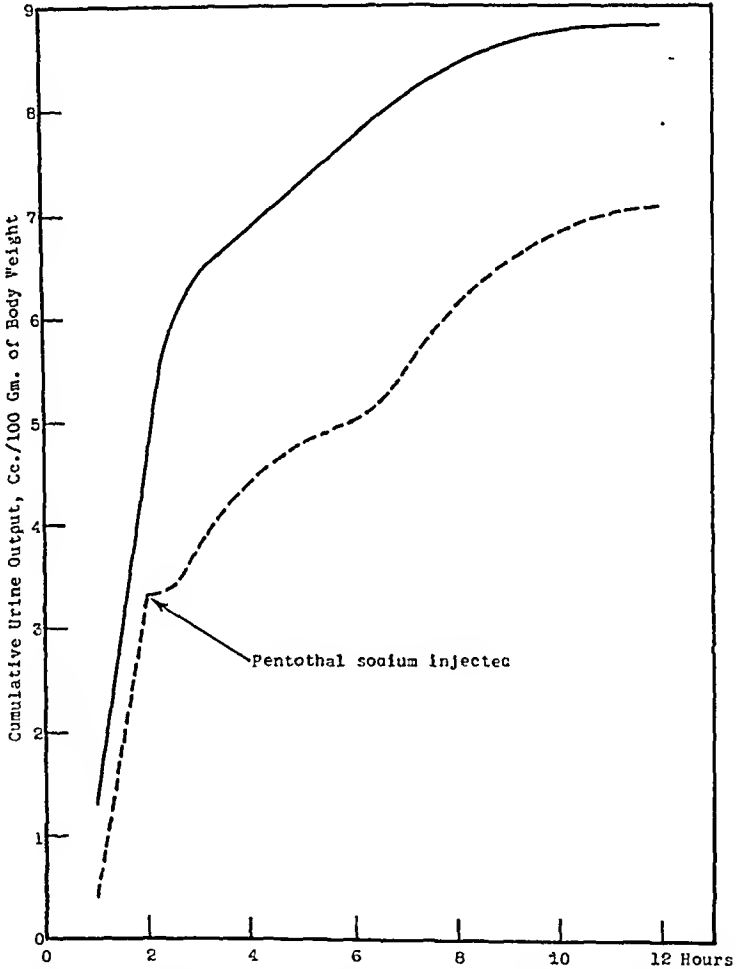


Fig. 3.—Effect of injected pentothal sodium on the urine output of white rats treated with theophylline with sodium acetate.

A number of similar experiments were also performed using theophylline with calcium salicylate (phylicin) in various doses, but antagonism to pentothal sodium antidiuresis could not be demonstrated.

*Influence of Mercurial Diuretics on Pentothal Sodium Antidiuresis.*—Eight hours before the start of the experiment two series of animals were given a priming dose of 0.75 mg. of mercupurin per hundred grams of

TABLE 4.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Mercupurin \**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	17	2.5	4.4	5.7	5.9	6.2	6.3	6.9	7.4	7.7	8.0	8.3	8.4	8.5	8.7
B (6 mg. of pentothal sodium /100 Gm. of body weight)	14	3.4	3.7	4.4	5.0	5.6	5.8	6.5	7.1	7.4	7.6	7.9	8.2	8.4	8.6

\* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was given intraperitoneally at the beginning of the experiment. For the doses of mercupurin, see the text.

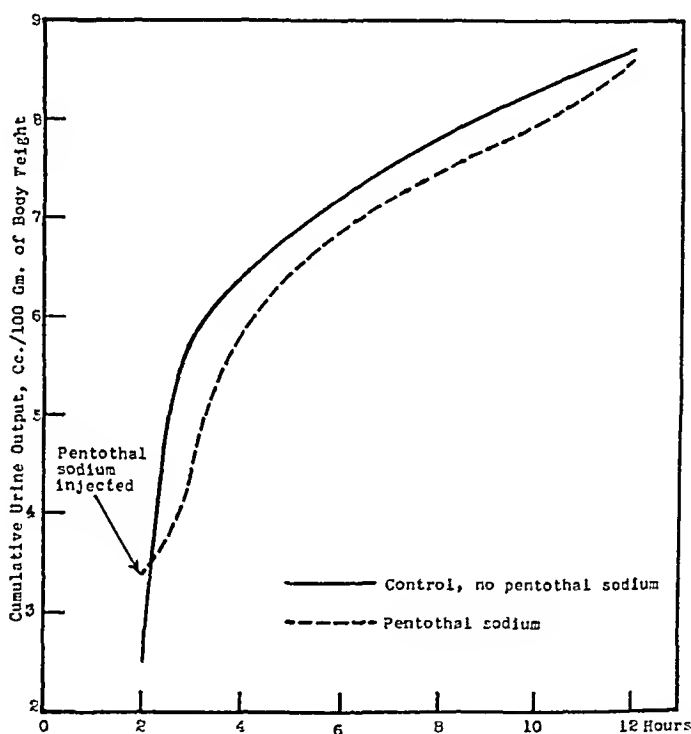


Fig. 4.—Effect of injected pentothal sodium on the urine output of white rats treated with mercupurin.

body weight. At the start of the experiment itself each animal was given a further dose of 0.75 mg. dissolved in the standard 10 cc. of 0.2 per cent sodium chloride solution. One series was given 6 mg. pentothal sodium per hundred grams two hours later.

Copious diuresis was induced in control animals by administration of mercupurin (table 4 A). In contrast to the completely negative effect of water, sodium chloride, urea and theophylline with sodium acetate and with calcium salicylate, however, mercupurin was at least partially effective in overcoming pentothal sodium antidiuresis (table 4 B). Thus, immediately after the injection of the barbiturate the usual temporary

inhibition of urine flow was observed, but this lasted only a short time, the urine flow rising within ninety minutes almost to the normal rate and level.

Comparable experiments were attempted using salyrgan, but the severe pain which the animals seemed to experience on injection of the drug forced their abandonment.

*Influence of Desoxycorticosterone Acetate and Adrenal Cortex Extract on Pentothal Sodium Antidiuresis.*—The action of a mercurial diuretic having its site of action on the renal tubular epithelium<sup>10</sup> in overcoming in part pentothal sodium antidiuresis suggested the use of another agent having the same site of action, the adrenal cortex extract.<sup>11</sup> The

TABLE 5.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Desoxycorticosterone Acetate\**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	10	2.5	3.6	...	5.3	...	5.9	6.6	7.0	7.4	7.9	8.3	8.5	...	8.8
B (6 mg. of pentothal sodium /100 Gm. of body weight)	10	2.7	3.2	...	3.6	...	3.7	4.0	4.8	5.9	6.7	7.1	7.5	...	8.3

\* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. All animals were given 3 mg. of desoxycorticosterone acetate in oil per hundred grams of body weight subcutaneously four hours before the start of the experiment.

effects of desoxycorticosterone acetate<sup>12</sup> and of adrenal cortex extract on pentothal sodium oliguria were therefore determined.

Four hours before the start of an experiment a number of animals were given subcutaneous injections of 3 mg. of desoxycorticosterone acetate in oil per hundred grams of body weight. Hypotonic solution of sodium chloride was then administered in the usual fashion, and at the

10. (a) Blumgart, H. L., and others: Action of Diuretic Drugs: Action of Diuretics in Normal Persons, *Arch. Int. Med.* **54**:40-81 (July) 1934. (b) Walker, A. M.; Schmidt, C. F.; Elsom, K. A., and Johnston, C. G.: Renal Blood Flow of Unanesthetized Rabbits and Dogs in Diuresis and Antidiuresis, *Am. J. Physiol.* **118**:95-110 (Jan.) 1937.

11. Silvette, H., and Britton, S. W.: Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Post-Pituitary Action, *Am. J. Physiol.* **123**: 630-639 (Sept.) 1938.

12. This compound was furnished by Dr. Ernst Oppenheimer, of Ciba Pharmaceutical Products, Inc.

end of two hours pentothal sodium (6 mg. per hundred grams) was injected into half the animals. Desoxycorticosterone acetate alone was without influence on the normal diuretic response of rats to 0.2 per cent sodium chloride solution (table 5 *A*) and also without effect on the course of pentothal sodium antidiuresis (table 5 *B*).

A supply of adrenal cortex extract made by a modified Swingle-Pfiffner method<sup>13</sup> was furnished by Dr. S. W. Britton, but when tested in the manner just described it was also found to be without effect either on control rats or on animals given pentothal sodium. It had previously been observed that adrenal cortex extract showed no diuretic effect when the rate of urine formation was already high.<sup>11</sup>

*Influence of Epinephrine Base in Oil on Pentothal Sodium Antidiuresis.*—Two series of animals were given intraperitoneal injections

TABLE 6.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Epinephrine Base in Oil\**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	10	3.1	4.1	4.8	5.1	5.4	5.5	5.7	6.0	6.4	6.7	6.8	6.8	6.9	6.9
B (6 mg. of pentothal sodium /100 Gm. of body weight)	10	3.5	3.8	4.7	5.1	5.2	5.5	5.7	5.8	6.1	6.3	6.4	6.4	6.8	7.0

\* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. For the dose of epinephrine base in oil, see the text.

of 0.2 per cent sodium chloride solution in the usual way and also simultaneous subcutaneous injections of epinephrine base in oil (0.5 mg. per hundred grams). Two hours later one series was given injections of pentothal sodium (6 mg. per hundred grams).

The administration of epinephrine to control animals resulted in a considerable increase in diuretic response during the early part of the metabolic period, which, however, was not sustained throughout the entire twelve hour period (table 6 *A*). The diuretic response of the animals given pentothal sodium was nevertheless identical with that of the controls (table 6 *B*; fig. 5), thus indicating antagonism of pentothal sodium antidiuresis by epinephrine.

13. Ehrenstein, M., and Britton, S. W.: The Purification of Adrenal Extracts and Isolation of an Activator of Male Sex Hormones, *Am. J. Physiol.* **120**:213-221 (Oct.) 1937.

*Influence of Solution of Posterior Pituitary on Pentothal Sodium Antidiuresis.*—The effect of this substance on the course of pentothal sodium antidiuresis was determined in a number of experiments. Two series of animals were given intraperitoneal injections of 1.5 units of posterior pituitary extract (0.15 cc. of solution of posterior pituitary U. S. P.) per hundred grams of body weight thirty minutes before the routine injection of 0.2 per cent sodium chloride solution. The antidiuretic effect of the posterior pituitary solution was apparent by the end of the second hour, at which time one of the series of animals received an injection of pentothal sodium (6 mg. per hundred grams). Simple

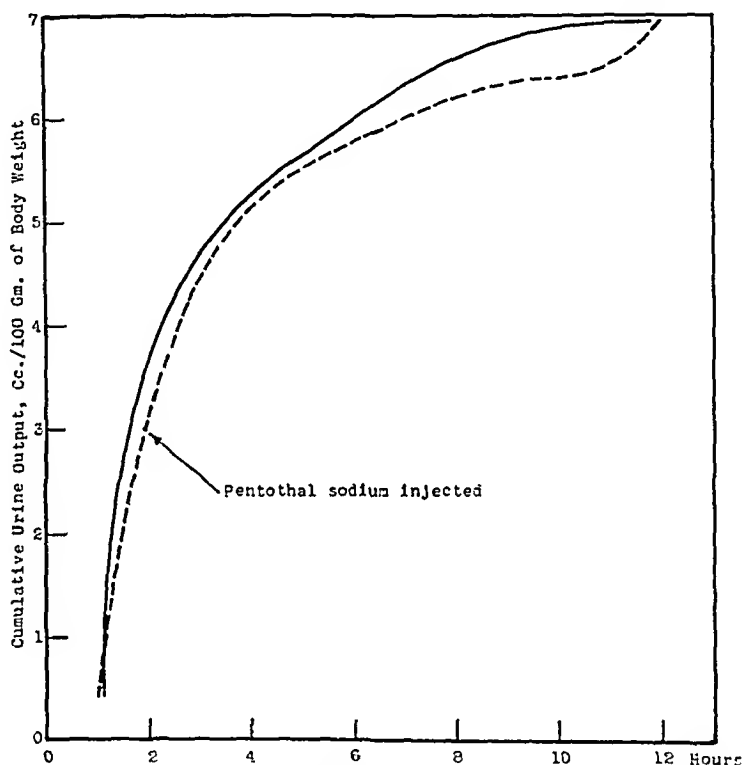


Fig. 5.—Effect of injected pentothal sodium on the urine output of white rats treated with epinephrine base in oil.

pituitary antidiuresis in the control animals lasted about eight hours, after which escape from pituitary inhibition occurred and a rapid rate of urine formation followed (table 7 *A*). Injection of pentothal sodium had an additive antidiuretic effect; inhibition of urine formation in animals receiving both posterior pituitary extract and pentothal sodium was greater and more prolonged than in those animals receiving posterior pituitary solution alone (table 7 *B*; fig. 6).

In two other series of animals the same dose of posterior pituitary solution was injected thirty minutes after the injection of pentothal

sodium rather than two and a half hours before, as in the previous experiments. But whereas subsequent injection of the latter drug merely reenforced the original pituitary antidiuresis, when pentothal sodium oliguria was induced first the subsequent injection of posterior pituitary solution had no antidiuretic effect (table 7 D) or even a slightly diuretic one compared with the control series (table 7 C; fig. 7). These results are in agreement with the well known observation that the injection of posterior pituitary solution into anesthetized animals is followed by diuresis rather than by inhibition of urine secretion.<sup>14</sup>

TABLE 7.—*Effect of Pentothal Sodium on Antidiuresis Caused by Solution of Posterior Pituitary \**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
I. Solution of Posterior Pituitary Injected 30 Minutes Before Start of Experiment (—0.5 Hr.)															
A (no pentothal sodium) (control series)	6	0.8	1.1	1.3	1.4	1.5	1.7	1.7	1.8	2.0	2.3	2.7	3.3	4.2	4.3
B (6 mg. of pentothal sodium /100 Gm. of body weight)	6	0.7	0.8	0.8	0.8	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.4	1.5	1.8
II. Solution of Posterior Pituitary Injected 30 Minutes after Injection of Pentothal Sodium (2.5 Hr.)															
O (no pentothal sodium) (control series)	18	1.7	2.2	2.7	3.2	3.5	3.9	3.9	4.4	4.4	4.5	4.6	4.7	4.9	5.0
D (6 mg. of pentothal sodium /100 Gm. of body weight)	18	1.7	1.8	2.3	3.2	3.9	4.2	4.7	4.9	5.1	5.2	5.3	5.3	5.4	5.5

\* All animals received 10 cc. of 0.2 per cent sodium chloride solution per hundred grams of body weight at the beginning of the experiment. For details of treatment with solution of posterior pituitary, see the text.

#### *Influence of Hypophysectomy on Pentothal Sodium Antidiuresis.*—

A number of male rats were completely hypophysectomized by Dr. E. L. Corey and were maintained after the operation for three to four weeks until the initial polyuria was succeeded by an essentially normal water intake and urine output.<sup>15</sup> At this time extensive atrophy of the gonads

14. Richards, A. N., and Plant, O. H.: Action of Minute Doses of Adrenalin and Pituitrin on Kidney, *Am. J. Physiol.* **59**:191-202 (Feb.) 1922. Nelson, E. E.: Diuretic Effect of Posterior Pituitary Extract in Anesthetized Animals, *J. Pharmacol. & Exper. Therap.* **52**:184-195 (Oct.) 1934.

15. Corey, E. L., and Britton, S. W.: Course of Diabetes Insipidus Following Hypophysectomy in the Rat, *Proc. Soc. Exper. Biol. & Med.* **46**:678-679 (April) 1941.

was evident, indicating complete removal of the pituitary. Such hypophysectomized animals were found to be extremely sensitive to pentothal sodium. Doses of 6 mg. per hundred grams, which were merely anesthetic in normal rats, were invariably fatal to hypophysectomized animals.

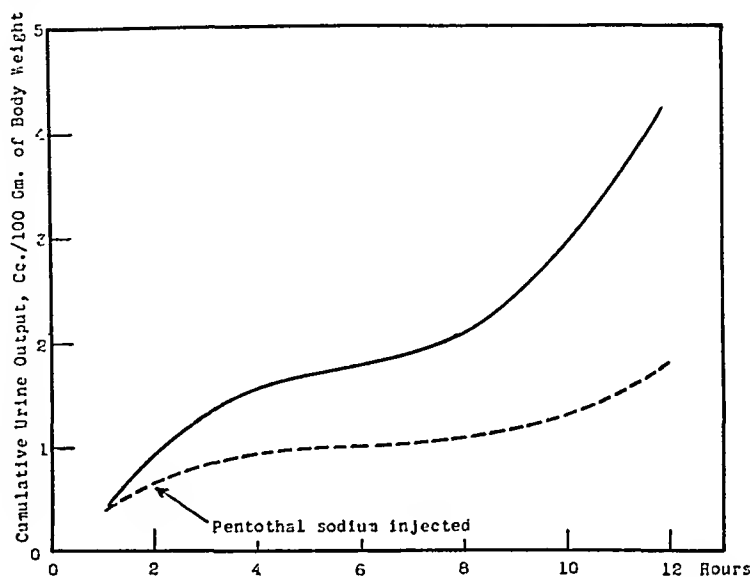


Fig. 6.—Effect of injected pentothal sodium on urine output of white rats after the administration of solution of posterior pituitary.

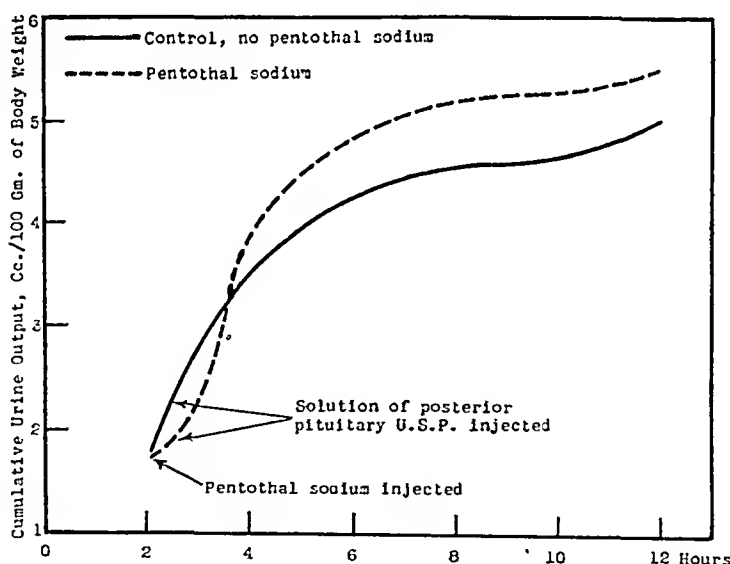


Fig. 7.—Effect of an injection of pentothal sodium followed by administration of solution of posterior pituitary on the urine output of white rats.

A dose of 4 mg. of pentothal sodium per hundred grams was found to be well sustained and fully anesthetic and was therefore employed in place of the standard dose of 6 mg. used in animals which had not been operated on.



TABLE 8.—*Effect of Pentothal Sodium on the Urine Output of Hypophysectomized Rats After Injection of Two-Tenths per Cent Sodium Chloride Solution \**

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	6	1.1	1.2	1.4	1.7	1.8	2.3	2.5	3.1	3.6	3.8	4.2	4.6	4.7	5.1
B (4 mg. of pentothal sodium /100 Gm. of body weight)	6	0.7	0.9	1.0	1.1	1.4	1.6	1.7	2.0	2.2	2.5	2.6	2.7	2.7	2.7

\* Ten cubic centimeters of saline solution per hundred grams of body weight was injected at the beginning of the experiment.

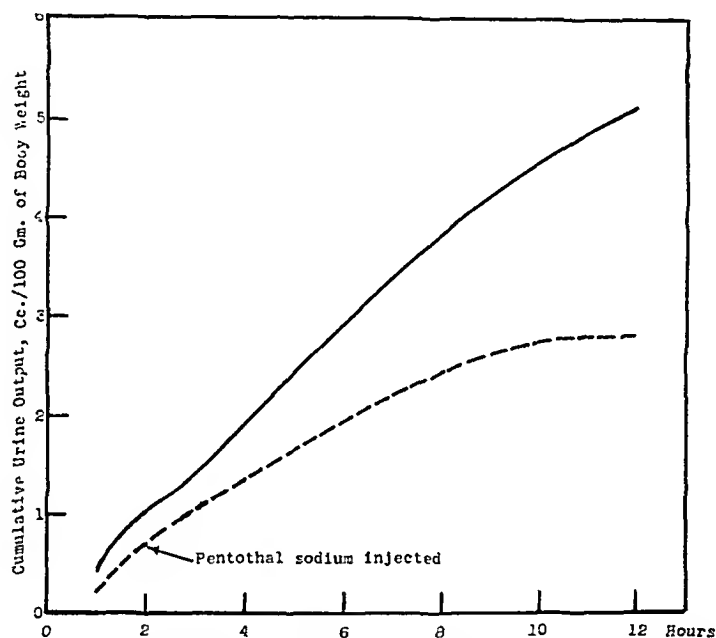


Fig. 8.—Effect of injected pentothal sodium on the urine output of long-surviving hypophysectomized white rats given 0.2 per cent sodium chloride solution.

A series of 6 long-surviving, completely hypophysectomized rats in good condition was given intraperitoneal injections of 10 cc. of 0.2 per cent sodium chloride solution per hundred grams, and a control diuretic response was established (table 8 A). Three days later the same animals were again tested, this time with an additional injection of 4 mg. of pentothal sodium two hours after the initial injection of fluid. Pentothal sodium antidiuresis was found to be as marked in these hypophysectomized rats as in normal animals which had not been operated on (table 8 B; fig. 8).

Many other hypophysectomized rats were tested individually for diuretic response, some with and some without subsequent injection of pentothal sodium. In all cases the animals receiving injections of the drug showed a definite inhibition of secretion of urine.

## COMMENT

It may be assumed for purposes of discussion that the principal influences leading to antidiuresis are the antidiuretic hormone of the posterior lobe of the hypophysis, renal tubular reabsorption of water and lowered blood pressure in the glomerulus, either primary or secondary as a reflection of general hypotension.

The mechanism by which barbiturates inhibit the secretion of urine has been described in a recent text book as "probably a central one on the hypophyseal-pituitary [sic] system."<sup>16</sup> De Bodo and Bloch in a preliminary report cited evidence which inferentially supports this view.<sup>17</sup> In their experiments phenobarbital in small nonanesthetic doses decreased the excretion of water approximately 50 per cent in normal dogs, but in dogs with diabetes insipidus (produced by the destruction of the entire neurohypophysis) this same dose had no effect on excretion of water. If animals so treated indeed do not show barbiturate antidiuresis, the conclusion is implicit that barbiturates, while depressing all other nervous centers, stimulate the hypophysis (or the hypothalamohypophyseal system) to secrete its antidiuretic hormone which by increasing renal tubular reabsorption of water results in decreased urine output. Any such selective stimulation seems highly improbable, especially since the hypothalamus appears to be one of the regions of greatest susceptibility to barbiturate depression,<sup>18</sup> and there is no evidence of it from the results of my experiments on hypophysectomized rats. In these long-surviving, completely hypophysectomized animals, which had passed the polyuric stage, the injection of pentothal sodium had the same antidiuretic effect as in normal animals. This indicates that the hypothalamohypophyseal system is not involved in the production of pentothal sodium oliguria in rats.

On the other hand, the site of pentothal sodium antidiuresis does not seem to be the renal tubular epithelium either, since this urinary inhibition is not antagonized by diuretics (by theophylline with sodium acetate or with calcium salicylate or by mercupurin) or by adrenal cortex extract which acts to inhibit renal reabsorption of water by the renal tubules. (The conclusions of Walker and associates<sup>10b</sup> are accepted, that xanthine diuresis is not accompanied by significant changes in renal blood flow or glomerular filtration but results from decreased tubular reabsorption of

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16. Goodman, L., and Gilman, A.: *Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941, p. 134.

17. De Bodo, R. C., and Bloch, H. I.: *The Effect of Narcotics on Diuresis*, *J. Pharmacol. & Exper. Therap.* **72**:4-5 (May) 1941.

18. Marshall, E. K., Jr.; Walzyl, E. M., and LeMessurier, D. H.: *Picrotoxin as a Respiratory Stimulant*, *J. Pharmacol. & Exper. Therap.* **60**:472-486 (Aug.) 1937.

fluid.) Mercurial diuretics,<sup>19</sup> theophylline with sodium acetate and with calcium salicylate<sup>20</sup> and desoxycorticosterone acetate<sup>21</sup> all antagonize pituitary antidiuresis, the site of which is agreed to be the tubular epithelium.<sup>22</sup> The fact that these agents do not also antagonize pentothal sodium antidiuresis renders it highly likely that the origin of this urinary inhibition does not lie in the renal tubules.

Diuretics which exert their effects by the osmotic retention of water within the renal unit (as sodium chloride and urea) are ineffective in overcoming pentothal sodium antidiuresis.

By the process of exclusion both of posterior pituitary and of renal factors in the production of pentothal sodium antidiuresis, the effect of injection of pentothal sodium in producing oliguria must therefore be due to alteration in glomerular blood pressure, either primarily or secondarily induced. Experiments on the effect of epinephrine in antagonizing this antidiuresis offer confirmation of this conclusion.

It is well understood that barbiturates, like other anesthetics, may affect urine secretion indirectly through the circulation. The hypotension which characterizes an overdose of a barbiturate results in oliguria or even anuria.<sup>23</sup> Rapid intravenous injection of pentothal sodium results in a sudden fall in blood pressure, which, however, soon returns to normal.<sup>24</sup> When the drug is intraperitoneally injected, as in these experiments, a fall in blood pressure occurs during the antidiuretic phase.<sup>25</sup> This lowered blood pressure apparently results from vasodilatation due to the depressant effect of barbiturates on smooth muscle.<sup>26</sup> Particularly in the case of pentothal sodium this leads to congestion, stasis and hemorrhage in the kidneys,<sup>27</sup> which would result in oliguria even

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19. Raab, W.: Effect of Pituitrin on Water Metabolism, Water Content of Blood and on Diuresis, *Wien. Arch. f. inn. Med.* **17**:471-512 (June) 1929.

20. Goodman and Gilman,<sup>16</sup> p. 649.

21. Corey, E. L., and Britton, S. W.: The Antagonistic Action of Desoxycorticosterone and Post-Pituitary Extract on Chloride and Water Balance, *Am. J. Physiol.* **133**:511-519 (July) 1941.

22. Silvette, H.: The Influence of Post-Pituitary Extract on the Excretion of Water and Chlorides by the Renal Tubules, *Am. J. Physiol.* **128**:747-753 (March) 1940.

23. Goodman and Gilman,<sup>16</sup> p. 134.

24. Gruber, C. M.: Effect of Anesthetic Doses of Sodium Thio-Pentobarbital, Sodium Thio-Ethamyl and Pentothal Sodium upon Respiratory, Heart, and Blood Pressure Changes in Experimental Animals, *J. Pharmacol. & Exper. Therap.* **60**: 143-173 (June) 1937.

25. Corey, E. L., and Silvette, H.: Unpublished data.

26. Gruber, C. M., and Gruber, C. M., Jr.: Segments of Excised Small Intestine as Affected by the Sodium Salts of Thioamyl, Thiopentobarbital, Pentobarbital and Evipal, *J. Pharmacol. & Exper. Therap.* **66**:16-17 (May) 1939.

27. Gruhzit, O. M.; Dox, A. W.; Rowe, L. W., and Dodd, M. C.: Pharmacologic Study of Certain Thiobarbiturates, *J. Pharmacol. & Exper. Therap.* **60**: 125-142 (June) 1937.

without the appearance of generalized hypotension. That the oliguria in the experimental animals was caused by local renal, or later by more generalized, hypotension is suggested by the fact that the urine flow could be maintained at control levels in these animals only by the injection of epinephrine in suitable concentration. In minute amounts epinephrine may cause constriction of the efferent renal arterioles before systemic vasoconstriction is evident,<sup>28</sup> thus leading to increased effective filtration pressure within the capillary tufts, even though no increase in systemic blood pressure occurs. This would seem to be the mechanism by which pentothal sodium antidiuresis was immediately overcome, followed by more generalized vasoconstriction as the concentration of injected epinephrine increased.

In connection with the antagonistic effect of epinephrine in overcoming pentothal antidiuresis, it is interesting to note that Gruber and associates<sup>29</sup> found that only epinephrine restored the normal rhythm in animals' hearts rendered arrhythmic by pentothal sodium. Experiments are now under way designed to correlate the course of pentothal sodium antidiuresis with the presence of pentothal sodium cardiac arrhythmia.

The results of the experiments herein described lead to the conclusion that pentothal sodium antidiuresis results from hypotension, either renal or general, brought about by the thiobarbiturate. Furthermore, the results also indicate that pentothal sodium does not exert any direct action either on the renal unit or on the hypothalamohypophyseal system in producing antidiuresis in rats.

#### SUMMARY

The injection of anesthetic doses of pentothal sodium (6 mg. per hundred grams body weight) into diuretic rats resulted in oliguria during the duration of the anesthesia. Subanesthetic doses (2-4 mg.) had no significant effect on urine output, save for temporary slight antidiuresis immediately following injection.

The course of pentothal sodium antidiuresis was not affected by the administration of diuretics (water, sodium chloride, urea or theophylline with sodium acetate or with calcium salicylate) or desoxycorticosterone acetate. Mercupurin counteracted in part the pentothal sodium oliguria.

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28. Hoskins, R. G., and Gunning, R. E. L.: Volume Changes and Venous Discharge in the Kidney, *Am. J. Physiol.* **43**:304-310 (May) 1917.

29. Gruber, C. M.; Haury, V. G., and Gruber, C. M., Jr.: Cardiac Arrhythmia, Characteristic Effect of Thio-Barbiturates (Pentothal, Thio-Pentobarbital, and Thio-Ethamyl) as Influenced by Changes in Arterial Blood Pressure, *J. Pharmacol. & Exper. Therap.* **63**:193-213 (June) 1938. Gruber.<sup>24</sup>

Injection of epinephrine in suitable concentration antagonized the antidiuretic effect of pentothal sodium and brought about a diuretic response identical with that of the control animals.

Completely hypophysectomized rats past the polyuric stage showed the same inhibition of water diuresis after injection of pentothal sodium as did animals which had not been operated on.

In animals anesthetized with pentothal sodium the injection of posterior pituitary solution was not followed by antidiuresis but by slight diuresis. Administration of pentothal sodium to rats rendered antidiuretic by injection of posterior pituitary extract resulted in more marked oliguria than that observed after injection of posterior pituitary extract alone.

From these and other considerations the conclusion was reached that pentothal sodium antidiuresis in rats results from hypotension, either renal or general. Furthermore, the results indicate that in the production of pentothal sodium antidiuresis the thiobarbiturate exerted no direct action on the renal unit or on the hypothalamicohypophyseal system.

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# Progress in Internal Medicine

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## GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1941 TO JULY 1942

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Much of the past year's literature on gastroenterologic subjects consists in confirmation or refutation of previously advanced ideas and observations. Such a state of flux is inevitable in consideration of the fact that experimental observations fundamentally represent a continuous process of addition, with occasional subtraction because of newer evidence. For this reason in any review it is necessary and wise to include much that is not entirely new but which sheds light on current ideas, many of which need modification and some of which need to be stressed again and again in order to establish the importance of fundamental clinical or physiologic principles. As in previous years, I will attempt to present a composite impression of many, but by no means all, of the articles that have appeared during the past year, avoiding as far as possible the inclusion of certain contributions which are merely repetitions of already recorded observations. An attempt has been made to separate the material into two major groups, one dealing with experimental or clinical observations on the functioning of the digestive tract and the other dealing largely with disease entities or with specific symptoms.

### GASTROINTESTINAL FUNCTION

*Motor.*—The relation between the higher levels of the central nervous system and the motor function of the gastrointestinal tract has been appreciated for a long time, but continued search is still indicated for a determination of the actual pathways that are involved and the way in which these pathways function. A study by Hesser, Langworthy and Kolb<sup>1</sup> of gastric activity released from cortical control is pertinent. These authors in experiments on cats recorded graphically definite alterations in gastric tone and motility following ablation of the cerebral motor cortices. Such alterations were demonstrable as greater per-

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1. Hesser, F. H.; Langworthy, O. R., and Kolb, L. C.: Experimental Study of Gastric Activity Released from Cortical Control, *J. Neurophysiol.* 4:274, 1941.

sistency, consistency and strength of stomach contractions along with increased tone of measured distention of the stomach. These changes were interpreted as evidence of a release from a regulating influence by the motor cortex. A marked stretch reflex with delayed relaxation of the stomach wall after sudden distention was also apparent. Similar modifications were noted in esophageal motility, and on the basis of previous experiments the authors quite properly suggest that the smooth muscle of the stomach and the esophagus is controlled by reflex pathways in the nervous system similar to those which control tone and contraction in the bladder. In this connection it is wise to recall the remarkable observations of Beaumont on St. Martin, with particular reference to motor and vascular changes in the stomach following emotional disturbances. The recent observations by Wolff and Wolf<sup>2</sup> on changes in the vascularization and the motor and secretory activity of the human stomach, as observed in a patient with a gastrostomy, are further confirmation of the intimate connection between the higher nerve centers and the function of the digestive tract. This study by Wolff and Wolf constitutes one of the most important visual demonstrations of such a correlation that has yet been made and provides the basis for a much clearer understanding of various transient or even more permanent changes that are to be encountered as manifestations of disease of the digestive tract in human beings. A somewhat metaphysical study by McGlade<sup>3</sup> may have a remote bearing on the preceding experiments. He studied the relation between the movements of the extremities occurring after the onset of sleep when certain foods were eaten one hour before going to bed. Each foot movement was found to coincide with the sound of the relaxing pyloric sphincter, suggesting evacuation of the stomach, and the author believes that he has secured evidence that the relation between these groups of movements and varied ingestion times not only was predictable in all cases but bore a definite time relation to dreams occurring at the end of the movements.

A type of conditioned reflex involving buccal sensation and alterations in gastric motor activity was studied in dogs by Bulygin,<sup>4</sup> who created chronic fistulas in the fundal and the pyloric part of the stomach and in the duodenum. Irritating substances introduced into the mouth produced

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2. Wolff, H. G., and Wolf, S.: Studies on a Subject with a Large Gastric Fistula: Changes in the Function of the Stomach in Association with Varying Emotional States, read at the meeting of the Association of American Physicians, Atlantic City, N. J., May 5, 1942.

3. McGlade, H. B.: The Relationship Between Gastric Motility, Muscular Twitching During Sleep and Dreaming, *Am. J. Digest. Dis.* **9**:137, 1942.

4. Bulygin, I. A.: Reflex Influence from the Oral Cavity upon the Gastric and Duodenal Movements, *J. Physiol. U. S. S. R.* **27**:331, 1939; abstracted, *Biol. Abstr.*, Sect. B **16**:3999, 1942.

an increase in gastric and duodenal movements in most instances, whereas water produced little if any change. If, however, water was introduced into a dog's mouth on the day following the experiments with irritating substances, the effect was the same as if an irritating substance had been placed in the mouth and appeared to be evidence of a conditioned reflex. After a certain number of days this reflex disappeared but could be renewed by repeating the experiment. The nervous pathways for the reflex regulation of intestinal pressure were studied in dogs by Youmans, Karstens and Aumann.<sup>5</sup> After determining by recording methods on Thiry fistulas that inhibition of one segment of the intestine could be obtained by distention of another segment, various observations were made after bilateral vagotomy at the level of the lower portion of the esophagus or at the midcervical region or after the splanchnic nerves were cut and the lumbar sympathetic chains were removed. What was called the "intestino-intestinal inhibitory reflex" was abolished by sympathectomy alone but was not noticeably altered by vagotomy. The conclusion was reached that only the sympathetic nervous system contains both afferent and efferent pathways for this particular reflex. The authors maintained that the regulation of intestinal motility by extrinsic nerves consists, in part, of reflex inhibition of the intestine as a result of stimuli arising from excessively strong contractions. One function of this reflex might be that of helping to keep the pressure within the intestine below the level which blocks blood flow through the vessels of the intestinal wall, a point that would have a direct bearing on some of the phenomena observed in intestinal obstruction. Whether sensory afferent pathways are confined to the sympathetic fibers, as has usually been thought to be the case and as is suggested by the foregoing results, is a matter for careful speculation and observation in relation to the phenomenon of pain arising from the digestive tract.

Recognition of the possibility that gastrointestinal motility may be importantly modified by deficiencies in one or more members of the vitamin B complex continues to be encountered in numerous articles, such as those by Mackie<sup>6</sup> and Martin and his collaborators.<sup>7</sup> Changes in the roentgen pattern of the small intestine may occur in a variety of conditions, and it is well known that they may be indicative, at times, of real deficiency disease. Mackie enumerates many of the conditions, such as sprue and steatorrhea, that are associated with a changed pattern

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5. Youmans, W. B.; Karstens, A. I., and Aumann, K. W.: Nervous Pathways for the Reflex Regulation of Intestinal Pressure, *Am. J. Physiol.* **135**:619, 1942.

6. Mackie, T. T.: Vitamin Deficiencies and the Small Intestine, *J. A. M. A.* **117**:910 (Sept. 13) 1941.

7. Martin, G. J.; Thompson, M. R., and DeCarvajal-Forero, J.: The Influence of Inositol and Other B Complex Factors upon the Motility of the Gastro-Intestinal Tract, *Am. J. Digest. Dis.* **8**:290, 1941.



and points out what may be a pertinent fact—that exactly the same pattern is presented by the intestine of the newborn infant. Since this “deficiency pattern” of the small bowel noted in early infantile life disappears completely during the child’s later development, it would seem that indirect evidence was available that is highly suggestive of a modification of the intrinsic nervous plexus covering intestinal motility. Degeneration of Auerbach’s and of Meissner’s plexus is known to occur in such a deficiency state as pellagra. By analogy, one may be justified in concluding that reversal of the mucosal pattern supposed to be characteristic of deficiency disease following the administration of vitamin B may be entirely due to the effect of some part of the complex on the intrinsic nerve supply of the intestine. Such a concept would be similar to the known results of thiamine administration on the changes in peripheral nerves encountered in patients with beriberi. Evidence seems to show that the administration of the vitamin B complex in the form of crude liver extract or yeast is much the most effective therapeutic method and indicates that such changes as have been observed may, in part at any rate, depend on some other factor than thiamine, riboflavin or nicotinic acid. Martin, Thompson and DeCarvajal-Forero<sup>7</sup> suggest, on the basis of animal experiments, that inositol and nicotinic acid are the members of the vitamin B complex directly concerned with motor function and that a balance or ratio of nicotinic acid or similar compounds to inositol is the nutritional factor which determines hypomotility or hypermotility. That the changes in gastrointestinal motility associated with a dietary lack of vitamin B<sub>1</sub> are not due to malnutrition alone is indicated in the animal experiments of Gershon-Cohen and his associates.<sup>8</sup> A comparison of the motility of the small bowel in animals on a vitamin B<sub>1</sub>-deficient diet and in a similar group under starvation conditions indicated that starvation alone produced minimal changes in the tonicity of the entire digestive tract.

Some experiments have been attempted to determine the effect of avitaminosis A on gastric emptying time, and in half of the experimental animals used by Herrin<sup>9</sup> the final emptying time of the stomach was strikingly increased under deficiency conditions. The results were variable, however, and it would seem that lack of vitamin A intake had little important influence directly on the motor activity of the stomach, except possibly as a reflection of a general nutritional disturbance. It is also of interest to note that in Herrin’s experiment the presence of avitaminosis A had no appreciable effect on the acid secretion of the stomach.

8. Gershon-Cohen, J.; Shay, H., and Fels, S. S.: B<sub>1</sub> Avitaminosis: Roentgenologic Studies of Gastro-Intestinal Tract in Rats on Vitamin B<sub>1</sub> Deficiency Diets, *Am. J. Roentgenol.* **46**:876, 1941.

9. Herrin, R. C.: Gastric Emptying Time and Acidity in Avitaminosis A in Dogs, *Am. J. Digest. Dis.* **7**:164, 1940.

By the use of balloons and the kymograph hypermotility of the human stomach was demonstrated by Hamilton and Curtis<sup>10</sup> during the clinical appearance of "gas pains," late postoperative nausea, "pylorospasm" secondary to ulcer, biliary colic, etc. During the clinical manifestations of these varying conditions gastric hypermotility occurred simultaneously with varying degrees of clinical distress. Moreover, the patients ceased to complain of pain or discomfort when the stomach was quiescent. Whether hypomotility was spontaneous or induced by atropine made no apparent difference. Such observations help to clarify the mechanism underlying symptoms common to various disease conditions and indicate the form of therapy needed. Further observations on the phenomena occurring during nausea are contributed by Ingelfinger and Moss.<sup>11</sup> Observations were made on 5 normal volunteers and on 15 patients, 5 of whom had organic disease of varying types. Kymographic records of duodenal activity were obtained after labyrinthine excitation or after the administration of morphine sulfate. By one of these two methods nausea was produced in most instances and was associated with a generalized contraction of the descending duodenum, which frequently resulted in the expulsion of balloons backward into the stomach, without, however, any demonstrable evidence of reverse peristalsis. The authors believe that duodenal spasm is a frequent concomitant of nausea and results in a pushing of the duodenal contents into the stomach by reversing the intestinal gradient. Necessarily, they point out, pylorospasm during nausea would seem to be impossible.

A prolonged initial depression of gastric motility and tone following the use of insulin is reported by Necheles, Olson and Morris<sup>12</sup>; this depression was coincidental with hypoglycemia. As the blood sugar rose to medium and slightly low values, the typical insulin hypermotility appeared. The authors explain this initial hypomotility on the basis of an increased epinephrine response to hypoglycemia and suggest, therefore, that the clinical use of insulin in cases of anorexia should be limited to the administration of rather small doses in order to avoid marked hypoglycemia.

Brown, Pendergrass and Burdick<sup>13</sup> compare the motor activity of the gastrointestinal tract in 24 patients with hyperthyroidism and 14 normal

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10. Hamilton, F. E., and Curtis, G. M.: Clinical Indications for Inducing Gastric Hypomotility, *J. A. M. A.* **117**:2228 (Dec. 27) 1941. Hamilton, F. E.: The Clinical Significance of Human Gastric Motility, *Ann. Surg.* **114**:153, 1941.

11. Ingelfinger, F. J., and Moss, R. E.: The Activity of the Descending Duodenum During Nausea, *Am. J. Physiol.* **136**:561, 1942.

12. Necheles, H.; Olson, W. H., and Morris, R.: Depression of Gastric Motility by Insulin, *Am. J. Digest. Dis.* **8**:270, 1941.

13. Brown, R. B.; Pendergrass, E. P., and Burdick, E. D.: The Gastro-Intestinal Tract in Hyperthyroidism, *Surg., Gynec. & Obst.* **73**:766, 1941.

persons and conclude that the following gastrointestinal changes are characteristic of hyperthyroidism: (1) an increased incidence of achlorhydria; (2) an increased prominence of gastric rugae; (3) an increase in the rapidity with which the stomach starts to empty; (4) a delay in gastric emptying following the initial increase; (5) increased tone of the small intestine with an abnormal pattern; (6) increased motility of the small intestine, and (7) a similar increase in tone and motility of the large intestine. A previously unpublished observation by Castleton<sup>14</sup> on the effect of artificial hyperthyroidism on the rate of rhythmic contractions both of intact and of excised small intestine of rabbits confirms the foregoing observations. This author believes it possible that the increase in the rate of rhythmic contractions is associated with an increase in the irritability of the bowel and that these changes may have something to do with the production of the diarrhea that is frequently noted in the thyrotoxic state. That the translation of the results of such animal experiments from one species to another or to human beings may not be appropriate is indicated in the experiments of Oppenheimer and Glycer,<sup>15</sup> who made observations on the motor activity of exteriorized intestinal loops in dogs. These loops included areas from high up in the jejunum to just above the ileocecal valve. The administration of thyroid in doses sufficient to elevate the basal metabolic rate 50 per cent did not alter the rate of contraction except in a segment just above the ileocecal valve. That increases in metabolic rate alone are insufficient to account for such motor changes is indicated by the fact that preparations of alpha-1,2,4-dinitrophenol given in doses sufficient to elevate the rate over 200 per cent did not increase the rate of contraction in the exteriorized loops. That some other mechanism may be involved in the diarrhea of hyperthyroidism is suggested, at any rate, by the report of Bartels.<sup>16</sup> In a group of patients suffering from diarrhea in association with hyperthyroidism and in whom the usual measures to control hypermotility of the bowel were ineffective, the administration of lipocaic restored normal intestinal function in the course of a short time. In 1 instance the return of hyperthyroidism was again associated with diarrhea, which was once more controlled by the use of lipocaic, suggesting the possible effect of lipocaic in supplementing the internal secretion of the alpha cells of the depleted pancreas.

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14. Castleton, K. B.: The Rate of Rhythmic Contraction of the Small Bowel of Rabbits as Influenced by Experimentally Produced Hyperthyroidism, *Am. J. Digest. Dis.* 8:473, 1941.

15. Oppenheimer, M. J., and Glycer, N. M.: The Effect of Elevated Metabolism on Rate of Intestinal Contractions, *Am. J. Digest. Dis.* 8:471, 1941.

16. Bartels, E. C.: Lipocaic in Treatment of Diarrhea of Hyperthyroidism: Preliminary Report, *West. J. Surg.* 49:439, 1941.

Larson<sup>17</sup> studied the effect of preparations of posterior pituitary on the motility of the large intestine in unanesthetized dogs. Giving solutions of posterior pituitary or pitocin intravenously resulted in a decrease in tone and motility of the upper and the lower portion of the large bowel. Pitressin was without effect. Subcutaneous or intramuscular injections of varied doses of solution of posterior pituitary or of pitressin usually caused only an increase in motility in the upper portion of the large bowel. Subcutaneous injection of pitocin had little or no effect on tone or motility.

The effect on motility of the exclusion of bile from the intestinal tract has been studied by Ackerman, Curl and Crandall.<sup>18</sup> In dogs with bile fistulas there was an increase in the rate of gastric evacuation and of the entrance of barium sulfate into the large intestine following a mixed meal. After a fat meal there was a slower gastric emptying time than in normal animals, which was increased by the administration of bile salts with the fat meal. These authors state that the suggestion that bile salts are an important factor in the regulation of the motility of the small intestine is not supported by their observations. It is possible that such observations indicate the need for a search for some other factor than the absence of bile salts as the one responsible for the rapid intestinal rate so frequently noted in patients with obstructive jaundice.

Studies made by Quigley and Meschan<sup>19</sup> with the tandem balloon method demonstrated that fatty acids or soaps introduced into the proximal portion of the intestine of fasting dogs inhibited the motility of the pyloric antrum sphincter and the duodenal bulb in a manner qualitatively similar to that in which natural fats acted. Such retardation of gastric evacuation apparently resulted from decreased antral peristalsis and occurred in spite of a relaxed sphincter. The evidence indicated that if natural fats were administered, they initiated the reaction and the products of digestion continued the influence. Analagous experiments are reported by Tidwell and Cameron,<sup>20</sup> the results of which indicate that the gastric inhibitory response to fat varies with its chemical composition, a finding similar to that noted by the preceding authors. The statement is made that there is a striking parallelism between the ease of

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17. Larson, E.: The Effect of Posterior Pituitary Preparations on the Large Intestine of the Unanesthetized Dog, *J. Pharmacol. & Exper. Therap.* **72**:363, 1941.

18. Ackerman, R. F.; Curl, H., and Crandall, L. A., Jr.: Gastrointestinal Tract Motility in the Absence of Bile, *Am. J. Physiol.* **134**:32, 1941.

19. Quigley, J. P., and Meschan, I.: Inhibition of the Pyloric Sphincter Region by the Digestion Products of Fat, *Am. J. Physiol.* **134**:803, 1941.

20. Tidwell, H. C., and Cameron, E. A.: The Relation Between the Chemical Structure of Fats and Their Ability to Produce Gastric Inhibition, *Bull. Johns Hopkins Hosp.* **70**:362, 1942.

absorption of a fat and its ability to produce gastric inhibition, which suggests that the absorption of fat from the duodenum is a prerequisite for the liberation of enterogastrone.

Tennent<sup>21</sup> concludes from animal experiments that alcohol delays gastric emptying and accordingly the absorption of dextrose. This delay in gastric emptying is attributed to the appearance of pylorospasm, which the author does not consider solely due to the irritating effect of alcohol on the gastric mucosa. When one considers that in these experiments the alcohol was administered by the intraperitoneal route, it seems pertinent to question whether the peritoneal irritation itself may not have contributed to alterations in motor activity. This may not have been the case, however, inasmuch as a certain length of time was allowed for the effects of alcohol to develop fully (intoxication) before dextrose was administered.

A comparison of the effect of liquid and of solid meals on intestinal activity has been made by Grindlay and Mann,<sup>22</sup> with observations on exteriorized loops of various portions of the small bowel. Sham feedings, the introduction of water and various liquid meals and the feeding of solid cooked meals all caused a typical sudden burst of motor activity, which was maintained, however, for more than a few minutes only in the case of a solid meal. Motor activity disappeared within a few minutes with a sham feeding and diminished rapidly after the administration of water or various liquids. The appearance of low grade, irregular segmentation waves and inconspicuous tonus changes was maintained for about half an hour in the case of water and slightly longer in the case of liquid meals. The motor response was sustained for hours after a solid meal, with resulting prominent irregular segmentation waves, tonus changes, tonus waves and occasional peristaltic waves, activity persisting in some instances for as long as twenty-four hours.

The effect of sodium amytal on gastric emptying was shown by Van Liere and Northup,<sup>23</sup> who noted an average decrease of almost 20 per cent when this drug was taken a short time before eating. An addition to studies on the effects of some spasmolytic substances on gastric function is to be found in the work of Lehmann and Knoefel.<sup>24</sup> A

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21. Tennent, D. M.: The Influence of Alcohol on the Emptying Time of the Stomach and the Absorption of Glucose, *Quart. J. Med.* **2**:271, 1941.

22. Grindlay, J. H., and Mann, F. C.: Effect of Liquid and Solid Meals on Intestinal Activity, *Am. J. Digest. Dis.* **8**:324, 1941.

23. Van Liere, E. J., and Northup, D. W.: The Effect of Sodium Amytal on the Emptying Time of the Normal Human Stomach, *J. Pharmacol. & Exper. Therap.* **73**:142, 1941.

24. Lehmann, G., and Knoefel, P. K.: The Effects of Some Spasmolytic Substances on Gastric Function, *J. Pharmacol. & Exper. Therap.* **74**:217, 1942.

comparison of the effects of atropine and similar substances on experimental cardiospasm and on gastric hypermotility caused by insulin was made. The comparative potency of such compounds seemed to vary similarly with their potency in depressing motility of the small intestine and with their potency in antagonizing the spasmogenic effects of acetylcholine on isolated intestine. Particular attention was paid to one compound (diethylaminoethylfluorene-9-carboxylate hydrochloride) chosen from a series of forty-four related compounds as the most promising for clinical trial. It was found that in terms of atropine this compound was about one-twentieth as potent in reducing gastric hypermotility and had much less effect in delaying gastric emptying and in reducing gastric secretion when given in one hundred times the dose. Such studies are of extreme importance in view of the fact that a real shortage of atropine and atropine derivatives exists at present because of the war. It is obviously important to procure potent spasmolytic substances to replace atropine if possible. An additional result of the foregoing studies is of interest as confirmation of previous observations, namely, that atropine and similar substances have little or no relaxing action on experimental cardiospasm. Such a finding is entirely confirmatory of the failure of atropine to produce beneficial effects in "cardiospasm" in human beings.

The effects of senescence on gastric motility have been studied by Van Liere and Northup.<sup>25</sup> By comparison with standards previously obtained on a large group of vigorous young adults, it was possible to conclude that no alteration of gastric emptying time could be demonstrated in a group of old men. The average age of the subjects was 70 years. In view of increased interest in geriatrics, such a study is of fundamental importance.

A comparative study on the mechanism of the action of prostigmine on intestinal motility was made on human beings and on dogs by Schwartz, Reingold and Necheles.<sup>26</sup> Their observations were made by means of kymographic records obtained after the introduction of a balloon into an intestinal fistula in human beings and by a somewhat similar maneuver in animals. The increased motor activity, which lasted from thirty to sixty minutes, that was noted in the human subjects after the use of prostigmine was not altered by the addition of acetylcholine. There were no serious or disturbing by-effects from the prostigmine. In the animal experiments it appeared that the effects of prostigmine on the intestinal musculature were twofold, namely, through stimulation

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25. Van Liere, E. J., and Northup, D. W.: The Emptying Time of the Stomach of Old People, *Am. J. Physiol.* **134**:719, 1941.

26. Schwartz, A. H.; Reingold, I., and Necheles, H.: A Study on the Mechanism of Action of Prostigmine on Intestinal Motility in the Human Being and in the Dog, *Surgery* **11**:746, 1942.

of the parasympathetic nerves and through direct stimulation of the intestinal musculature. It was impossible to abolish the action of prostigmine by the use of atropine, although the effect obtained by acetylcholine could be so abolished. The therapeutic use of prostigmine in paralytic ileus is thus justified by these investigators, who suggest a dose of prostigmine based on the weight of the individual patient. Patients weighing under 125 pounds (57 Kg.), they believe, should receive proportionately less than 1.0 mg. of prostigmine methylsulfate, a dose which seems to be adequate for persons at or above that weight.

Because of its application to optimum preparation of subjects for roentgen examination of the colon the study of Bruck and Fruchter<sup>27</sup> is of interest. Control observations were made on a group of 15 young adults after the ingestion of a barium sulfate meal, and subsequently repeated observations were made after the administration of a barium sulfate meal combined with one of several commonly used laxatives. The effects of fluidextract of cascara sagrada, compound licorice powder, magnesium citrate, magnesium sulfate and castor oil were thus studied. The last three laxatives produced some delay in gastric emptying time, and all of the laxatives studied produced an initial irritability of the proximal portion of the jejunum, lasting one to three hours. With magnesium sulfate there was a definite delay in the passage of the meal through the small intestine, but the other laxatives produced moderately increased motility of the small intestine. Of the preparations used, compound licorice powder and castor oil proved the most satisfactory in completely emptying the colon and are to be preferred for colonic cleansing in routine preparation for roentgen studies. In spite of the production of numerous bowel movements more barium sulfate was retained at the end of forty-eight hours after the administration of magnesium salts than during a control observation. These studies are supplementary to observations reported previously by Oppenheimer and Mann and reviewed a year ago.<sup>28</sup>

Necheles and Olson<sup>29</sup> report the effects of trauma and traumatic shock on gastrointestinal motility and secretions, and the results of this study are compared with those previously obtained on the effects of burns, after which there was an increase of gastric motility and in some animals a considerable increase in the volume and the acidity of the

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27. Bruck, S., and Fruchter, J. M.: Influence of a Single Dose of Commonly Used Laxatives on Gastro-Intestinal Motility: A Comparative Study, *Radiology* **38**:145, 1942.

28. Jones, C. M.: Gastroenterology: A Review of Literature from July 1940 to July 1941, *Arch. Int. Med.* **68**:763 (Oct.) 1941.

29. Necheles, H., and Olson, W. H.: Experimental Investigation on the Effects of Trauma and Traumatic Shock on Gastrointestinal Motility and Secretions, *Am. J. Physiol.* **136**:32, 1942.

gastric secretions. In these experiments gastric motility was slightly increased for short periods when the blood pressure of traumatized animals was above 80 mm. and for somewhat longer periods and to a greater extent when the blood pressure declined further. This did not compare with the intensity of gastric activity that was noted after burns. In none of the burn experiments was there a depression of gastric motility, a phenomenon which was encountered in a number of the experiments with trauma. The authors believe that the moderate increase in gastric motility following traumatic shock may be related to anoxemia as both became more apparent with a lower blood pressure, but they point out that the anoxemia of the stomach may be more dependent on vasomotor regulation than on systemic blood pressure. Various degrees of traumatization had no significant effect on the gastric secretion, and the depressant effect of burns on salivary, pancreatic and biliary secretions was considerably greater than that associated with mechanical trauma. It would seem pertinent to point out that such animal experiments necessarily fail to take into account the factor of pain which is almost always associated with traumatic shock or severe burns in human beings. This cannot be entirely disregarded as a possible important factor in the production of various vasomotor disturbances, which might lead to motor or secretory changes in the stomach and thus have a bearing on the production of ulcer.

Studies by Wasteneys, Crocker and Hamilton<sup>30</sup> made use of an ingenious reentrant fistula in dogs, situated just below the junction of the duodenum and the jejunum, as a means of investigating the digestion of various food substances. Of the observations and suggestions reported, one is extremely pertinent; namely, it is not justifiable to interpret "emptying time" (as obtained from roentgen studies) in terms of relative digestibility of food stuffs. It is obvious from the numerous reports that have been made on gastric emptying time after roentgen studies and on the determination of "percentage of digestion," that conclusions based on what is largely a motor function are in no way adequate to cover entirely the question of digestion and digestibility.

*Secretory.*—A most competent discussion of the internal secretions of the gastrointestinal tract is to be found in an article by Ivy.<sup>31</sup> This article brings up to date the known facts in regard to this phase of the physiology of the digestive tract and outlines the implications, therapeutic and otherwise, in a satisfactory manner. The work is too detailed

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30. Wasteneys, H.; Crocker, B. F., and Hamilton, P.: Studies of Digestion in the Dog, *Am. J. Physiol.* **135**:6, 1941.

31. Ivy, A. C.: Glandular Physiology and Therapy: Internal Secretions of the Gastrointestinal Tract, *J. A. M. A.* **117**:1013 (Sept. 20) 1941.



to warrant complete discussion in the present review but deserves a careful reading by those interested in the physiology of the gastrointestinal tract. The secretory response of the gastric glands to gastrin, the stimulation of pancreatic secretion by secretin, the evacuation of the gallbladder by cholecystokinin, the inhibition of gastric motility and secretion by enterogastrone, the stimulation of the secretion of succus entericus and the possible augmentation of the movements of the intestinal villi to promote intestinal absorption by villikin are all discussed as proved or probable physiologic examples of the humoral control of the digestive processes. Mention is also made of the possibility that the gastrointestinal tract may harbor an "insulin synergist" affecting carbohydrate metabolism. This hypothetic substance, for which the name duodenin has been suggested, is supposed to have a stimulating effect on the islands of the pancreas. Ivy points out correctly that none of the internal secretions of the gastrointestinal tract has been demonstrated to have therapeutic value. Histamine, if it is gastrin, and secretin possess diagnostic value; cholecystokinin is of potential diagnostic value; enterogastrone and urogastrone (*vide infra*) possess therapeutic promise. In a discussion of the humoral stimulation of gastric secretion, Gregory and Ivy<sup>32</sup> present evidence that there are at least two components in the humoral stimulation of a transplant of the gastric fundus by a meal—one liberated from the gastric mucosa by the presence of secretagogues and the other from the mucosa of the small intestine by the presence of food or secretagogues. The results of experiments in which the mucosa of one or the other of the pouches of a two pouch preparation was anesthetized by procaine hydrochloride have provided evidence that the gastric component of humoral stimulation is hormonal in nature. No such experiments have been performed in connection with the intestinal phase. The result of one experiment, which is subject to confirmation, in which the pyloric region of the gastric mucosa was removed from the main gastric pouch of the two pouch preparation, leads to the conclusion that the presence of this region of the stomach in the main gastric pouch is not essential for the demonstration of the humoral response of the transplant to perfusion of the main gastric pouch with a solution of secretagogues. It would seem that confirmation of this particular phase of the experiment might have an important bearing on the question as to how much of the stomach is to be removed at subtotal resection in order to obtain the most favorable results from the point of view of acid secretion.

A further theoretic discussion on the role of enterogastrone, a substance obtained from the intestinal mucosa and one which inhibits gastro-

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32. Gregory, R. A., and Ivy, A. C.: The Humoral Stimulation of Gastric Secretion, *Quart. J. Exper. Physiol.* **31**:111, 1941.

intestinal motility and secretion, is given by Quigley,<sup>33</sup> who emphasizes the necessity for further studies on the physiologic activity of this substance before attempting to assess any possible therapeutic value it may have in the therapy of ulcers. Further investigations on the gastric secretory depressant occurring in urine are presented by Friedman and Sandweiss.<sup>34</sup> These investigators observed the effect of this substance on gastric secretion in dogs with Heidenhain pouches and found that it inhibited the gastric secretion stimulated by insulin, histamine and food. They believe that the mechanism involved is not known but that the site of action is on the gastric secretory cells. The preliminary acute experiments showed the inhibitory effect to be absent in dogs which have had the whole of the small intestine removed, suggesting that such action on the gastric glands is indirect. The authors point out that a consideration of the available data published by themselves, by Ivy and his associates and by Necheles leads to the conclusion that a substance which inhibits gastric secretion when administered intravenously is excreted in the urine of normal men and women and in that of dogs. They believe that this inhibitory effect of urine extract is not due to pyrogenic substances. The nature of the gastric secretory depressant substance is unknown, but because it is relatively thermostable it does not appear to be an enzyme. It has not yet been proved that the integrity of the small intestine is essential for the inhibitory effect of enterogastrone, although it appears that the inhibitory effect of urogastrone is mediated by the small intestine. Gray and his collaborators<sup>35</sup> have been led to the conclusion that there is no support for the view that urogastrone and enterogastrone are identical. The evidence suggests the importance of the gastrointestinal tract for the regulation of urogastrone excretion. That the output of urogastrone is reduced below normal in patients with ulcer is apparently a proved fact. The action of urogastrone is apparently specific for the stomach, for it is without effect on salivary secretion and on urinary secretion. Both in animals and in man Gray and others have shown that this principle, when given parenterally, reduces the volume and the acidity of gastric secretion after the administration of histamine. Whether the same agent is responsible for mild motor inhibition as well has not been established.

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33. Quigley, J. P.: Enterogastrone—Significant Steps in Development of the Present Conceptions, *Am. J. Digest. Dis.* **8**:363, 1941.

34. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, *Am. J. Digest. Dis.* **8**:366, 1941.

35. Gray, J. S.; Culmer, C. U.; Wells, J. A., and Wieczorowski, E.: Factors Influencing the Excretion of Urogastrone, *Am. J. Physiol.* **134**:623, 1941. Gray, J. S.: Present Status of Urogastrone, *Am. J. Digest. Dis.* **8**:365, 1941. Gray, J. S.; Wells, J. A., and Ivy, A. C.: Gastric Secretion in Enterectomized Dogs *ibid.* **8**:353, 1941.

The apparent excretion of urogastrone is decreased by removal of the small bowel, but there is no proof as yet that the inhibitory principle occurring in urine originates entirely in the small intestine, and it is quite possible that this is not the case. The obvious therapeutic implications inherent in this substance, which inhibits gastric secretory, and possibly motor, function, have yet to be explored from the point of view of prevention or cure of ulcer.

Sandweiss and Friedman<sup>36</sup> have studied the effect on histamine-stimulated gastric secretion in Mann-Williamson dogs of the gastric secretory depressant factor in extracts of urine of normal and of pregnant women. The range of gastric acidity was the same both in the treated and in the untreated animals, and it would appear that the prolongation of survival time in the treated animals was not due to the inhibition of gastric acid but to the administration of the urine extract. These authors suggest that the urine extracts exert beneficial effects through stimulation of active fibroblastic proliferation and epithelialization of the ulcer, a process which can occur in the presence of normal gastric acid juice. A good deal of careful and discriminating work must be done before the final status either of urogastrone or of enterogastrone can be determined, but it is obvious that this type of physiologic approach to the ulcer problem may well be of fundamental importance.

Further evidence of the influence of hormonal control of gastric secretion is to be found in experiments of Schiffrin,<sup>37</sup> who studied the relation between the parathyroid and the gastric glands in dogs. As has already been shown, the administration of parathyroid in amounts sufficient to increase calcium in the blood serum to any important degree produced a decrease in the volume and the acidity of the gastric contents after stimulation by histamine or by a test meal, and such an inhibition persisted after the serum calcium had returned to normal levels. Experiments were made on a Pavlov pouch dog and on a dog with an esophagotomy and a gastric fistula. The volume of the response to sham feeding and to administration of insulin and histamine was decreased, although there were no persistent after-effects, as in the previous experiment. In both instances, however, the concentration of pepsin in the gastric juice was definitely increased. In a Heidenhain pouch dog, such measures, on the other hand, increased the volume, the acidity and the chloride content of the gastric juice but had no effect on pepsin, and a similar effect was observed after the use of irradiated ergosterol. After thyroparathyroidectomy the volume of gastric secre-

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36. Sandweiss, D. J., and Friedman, M. H. F.: Is the Beneficial Effect of Urine Extracts on Mann-Williamson Ulcers Due to the Gastric Secretory Depressant in Urine? *Am. J. Digest. Dis.* 9:166, 1942.

37. Schiffrin, M. J.: Relationship Between the Parathyroid and the Gastric Glands in the Dog, *Am. J. Physiol.* 135:660, 1942.

tion was increased and the concentration of pepsin was decreased in all of the different preparations, but this result could be reversed by the intravenous injection of calcium lactate or the subcutaneous administration of solution of parathyroid. Thyroxin had no effect on the gastric secretory response.

A rather interesting gastroscopic observation on gastric secretory activity was made by Lerner, Asher and Andrews.<sup>38</sup> They watched the appearance of neutral red in the gastric mucosa after parenteral injection of the substance. In fasting animals only scattered pinpoint areas could be seen, and they were limited almost entirely to the fundus and the upper portion of the body. No dye was seen at the cardia, antrum or pylorus. It would seem from this observation that in the fasting state few of the pepsin-secreting and hydrochloric acid-secreting cells were functioning, a not illogical but nevertheless interesting finding.

By means of careful experiments on dogs with vagotomized gastric pouches, Gray and Bucher<sup>39</sup> made a detailed study of the composition of the gastric juice as a function of the rate of secretion. Repeated injections of histamine provided the stimulus for secretory activity, and accurate determinations of basic and of acid ions were obtained. By a detailed analysis of these various components, it was shown that the composition of gastric juice can vary only between the limits set by its two main sources—the parietal and the nonparietal cells. Since the nonparietal component is secreted at a slow and practically constant rate, whereas the parietal component is secreted at rates which vary widely with the dose of histamine, the authors conclude that the composition of the gastric juice is a function of its rate of secretion. The only constant element was that of potassium, the concentration of which remained practically the same throughout the observations.

In experiments on animals with cannulated gastric and duodenal fistulas, Berk, Thomas and Rehfuß,<sup>40</sup> studied the reaction and neutralizing ability of the pyloric antrum and the first portion of the duodenum after high carbohydrate and high fat meals. With an Ewald meal the contents of the first portion of the duodenum displayed a neutral-

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38. Lerner, H. H.; Asher, L., and Andrews, K.: The Excretion of Neutral Red by the Gastric Mucosa as Visualized Gastroscoically, *Am. J. Digest. Dis.* **9**:109, 1942.

39. Gray, J. S., and Bucher, G. R.: The Composition of Gastric Juice as a Function of the Rate of Secretion, *Am. J. Physiol.* **133**:542, 1941.

40. Berk, J. E.; Thomas, J. E., and Rehfuß, M. E.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, *Am. J. Physiol.* **136**:157, 1942; The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs, *ibid.* **136**:285, 1942.

izing, buffering and diluting capacity apparently in excess of physiologic needs,  $p_H$  values in both the pyloric antrum and the duodenal bulb varying independent of titratable total acidity. A high fat feeding, as is known, diminished gastric acidity and enhanced the excess neutralizing ability of the contents of the first portion of the duodenum over fairly prolonged periods. The authors feel that this decrease in duodenal acidity following the administration of cream was only partly due to the inhibitory effect of fat on gastric secretion. They believe that the acidity of the contents of the duodenal bulb in a normal dog is largely determined by the type of food undergoing digestion and is related only in part to the acidity of the gastric contents. In a normal dog cream appears to be a much more effective duodenal antacid than some of the commonly employed antacid medications. Such results, however, await the further elucidation that may possibly be obtained from a more accurate knowledge of the inhibitory effects of such substances as enterogastrone. Another method of approaching the subject of gastric secretory activity is described by Mann, Grindlay and Mann.<sup>41</sup> By an ingenious operative procedure on dogs it was possible to make chloride determinations on arterial and on gastric venous blood during the process of digestion. During the rapid secretion of hydrochloric acid by the gastric mucosa appreciable differences in the chloride concentration in the systemic and the gastric venous blood were observed only occasionally. These differences appeared to depend mainly on variations in the cell chlorides.

Grant<sup>42</sup> has contributed further information on the buffering substances in gastric secretion by studies on gastric mucus. In cats she found that mucus from surface epithelial cells and from the cells producing it in the vagal type of secretion is an immediate source of calcium in gastric secretions. Actively functioning peptic or parietal cells do not appear to be necessary for its production. The theory that mucus is an important factor for the reduction of gastric acidity is supported by direct evidence. She has been led to believe that an important factor responsible for variations in calcium content and acidity of gastric secretions in the presence of varying amounts of mucus in secretions of different types. Calcium is liberated from the mucus in a reaction associated with the reduction of acidity and is an index of this reaction. Further evidence that the mucoid secretion of the stomach is of importance in lowering the acidity and the total chloride concen-

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41. Mann, F. D.; Grindlay, J. H., and Mann, F. C.: The Withdrawal of Chloride from the Blood by the Gastric Glands, *Am. J. Digest. Dis.* 8:451, 1941.

42. Grant, R.: Calcium in Gastric Mucus and Regulation of Gastric Acidity, *Am. J. Physiol.* 135:496, 1942.

tration of the gastric juice was obtained by Babkin and his associates<sup>43</sup> as a result of the application of acetic acid solutions to the gastric mucosa. When this procedure was followed by the injection of histamine, a diminished volume of gastric secretion, with a lowering of the total chloride concentration and the free and the total acidity, was constantly noted, and this was associated with a striking increase in mucus secretion, which the authors believe was responsible for the alterations obtained. Certainly such findings would seem to indicate clearly one of the protective mechanisms inherent in the stomach that is more or less effective in the presence of mucosal irritation or inflammation, as previously pointed out by Fogelson and others.

Sixteen amino acids were studied by Thomas<sup>44</sup> to determine whether they caused gastric inhibition when placed in the small intestine. Only the monoamino-monocarboxy acids caused gastric inhibition regularly when administered in neutral salts, and the inhibitory effect was roughly proportional to their molecular weights. The dicarboxy acids and the diamino acids inhibited secretion only when administered as free acids without neutralization.

The effect of heavy irradiation of the stomach is well known to decrease its secretory activity, and observations made by Streicher<sup>45</sup> showed that pathologic changes following such a procedure involved chiefly the secretory epithelium of this organ. He also produced evidence that hepatic damage secondary to direct high voltage irradiation or caused by the use of carbon tetrachloride not only produced intrahepatic changes but, at the same time, depressed the acidity of the gastric juice. In these experiments the gastric juice obtained from a Pavlov pouch was apparently highly buffered, and it appeared that this buffering again was due to chemical constituents (perhaps protein) which were recognizable at hydrogen ion concentrations between 3 and 5 and between 6 and 7.

A study of the functions of the stomach following partial pyloric obstruction with and without gastroenterostomy was made by Neuwelt and associates<sup>46</sup> after an operative procedure on dogs. After a prolonged control period of observation following the production of pyloric stenosis, gastroenterostomies were performed and gastric secretory activity was

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43. Babkin, B. P.; Hebb, C. O., and Krueger, L.: Changes in the Secretory Activity of the Gastric Glands Resulting from the Application of Acetic Acid Solutions to the Gastric Mucosa, *Quart. J. Exper. Physiol.* **31**:63, 1941.

44. Thomas, J. E.: Gastric Inhibition Caused by Amino Acids in the Small Intestine, *Am. J. Physiol.* **135**:609, 1942.

45. Streicher, M. H.: Effect of Hepatic Damage on Gastric Acidity, *Arch. Surg.* **43**:74 (July) 1941.

46. Neuwelt, F.; Medoff, J.; Patredjl, J., and Necheles, H.: A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastro-Enterostomy, *Am. J. Digest. Dis.* **8**:310, 1941.

compared with that during the control period. The results were variable. There was no change in the volume or the acidity in some animals after enterostomy; in others there was an increase, and in a third group, a decrease. Neither peptic nor anastomotic ulcers were observed in any of the animals. The conclusion was reached that gastroenterostomy in dogs combined with partial pyloric stenosis cannot be relied on to produce rapid emptying of the stomach or reduced gastric acidity. Such a finding may help to explain many of the failures attributed to a gastroenterostomy in the presence of ulcer, but a complete comparison is not entirely permissible, inasmuch as none of these dogs had an ulcer at any time.

A rather complete review of the various experimental procedures that have been carried out on the stomach in an attempt to produce pernicious anemia has been made by Petri and Jensenius.<sup>47</sup> As these authors point out, no operative procedures on animals have been developed which will result in the production of a pernicious anemia state, although various types of anemia, depending on the species of animal and kind of operation, have resulted from various maneuvers. Because of the discrepancy existing between results obtained by various investigators, the writers urge a still further study of the biologic foundation underlying such a condition as addisonian anemia. They consider that failure to reproduce such a condition in animals is due to the fact that either the site of formation of the intrinsic factor has not been adequately controlled by operative procedures or the correctness of Castle's theory has to be questioned. Fox and Castle,<sup>48</sup> using various preparations of hog and of human stomach, have attempted to determine whether the material present in the preparations and possessing a blood-forming activity in addisonian pernicious anemia could be used to define the site at which the intrinsic factor was secreted and whether observations based on the hog stomach were applicable to the human stomach. From their observations and those of Meulengracht it appears that the antianemic potency of the pyloric portion of the hog stomach indicates the main site at which the intrinsic factor is secreted in that animal but that in man areas containing the fundus type of gland and not the "pyloric gland organ" are the important sites at which the intrinsic factor is secreted. This site coincides with the site of the degenerative process seen in microscopic preparations of the stomach in pernicious anemia in human beings. It is important to stress such

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47. Petri, S., and Jensenius, H.: Experimental Studies on Production of Pernicious Anemia by Operation on Digestive Tract: Survey of Results of Total Gastrectomy and Resections of Stomach, *Acta med. Scandinav.* **106**:274, 1941.

48. Fox, H. J., and Castle, W. B.: Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IX. Difference in Site of Secretion of Intrinsic Factor in Hog and in Human Stomach, *Am. J. M. Sc.* **203**:18, 1942.

species differences in relation to animal experimentation, and such a finding, of course, would seem to explain the infrequency with which macrocytic anemia occurs in gastric resections in man, inasmuch as under such circumstances the cardiac portion of the human stomach is saved and may provide an adequate source of the intrinsic factor. In spite of the known secretory deficiencies existing in patients with Addisonian pernicious anemia, it is of some interest that Witebsky and associates<sup>49</sup> were able to demonstrate that the gastric juice of patients with pernicious anemia contains blood group-specific substances in the same large amounts as normal gastric juice.

*Absorptive.*—The complicated process of phosphorylation in relation to intestinal absorption still requires much study before it can be finally elucidated. To those interested in this complex and still hypothetical phenomenon the study of Beck<sup>50</sup> on some of the details of the phosphorylation hypothesis of dextrose absorption by intestinal mucosa warrants examination. In this work an analysis was made of various phosphate fractions in intestinal mucosa after absorption in order to determine the relative importance of various phosphorus compounds in dextrose absorption. On the basis of barium separation procedures and "fructose" determinations it seemed that most of the absorptive increase in the intestinal mucosa was due to an accumulation of a hexose monophosphate ester.

Barnes, Miller and Burr,<sup>51</sup> using spectroscopically distinguishable conjugated fatty acids of corn oils, made a study of the absorption and transport of the methyl esters of fatty acids across the intestinal mucosa of rats. The results showed no apparent parallelism between the rate of fatty acid incorporation into mucosa phospholipids and transport. Winter and Crandall,<sup>52</sup> by using the angiotomy technic in dogs, have thrown some new light on the question of the portal absorption of fatty acids, samples of blood being drawn simultaneously from the portal and the hepatic vein and from the femoral artery before and during fat absorption. No significant arterioportal or hepatic inflow-outflow differences in fatty acid content could be demonstrated during fat absorption. It would seem from such results that fat absorption from the intestine by way of the portal vein is negligible.

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49. Witebsky, E.; Klendshoj, N. C., and Vaughan, S. L.: Occurrence of Blood Group Specific Substances in Gastric Juice of Patients with Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **49**:633, 1942.

50. Beck, L. V.: Organic Phosphate and "Fructose" in Rat Intestinal Mucosa, as Affected by Glucose and Phlorhizin, *J. Biol. Chem.* **143**:403, 1942.

51. Barnes, R. H.; Miller, E. S., and Burr, G. O.: The Absorption and Transport of Fatty Acids Across the Intestinal Mucosa, *J. Biol. Chem.* **140**:233, 1941.

52. Winter, I. C., and Crandall, L. A., Jr.: The Question of the Portal Absorption of Fatty Acids, *J. Biol. Chem.* **140**:97, 1941.



Alterations in the absorptive capacity of the small intestine in the presence of deficiency disease are known to occur and undoubtedly form the basis of some of the nutritional disturbances seen in such conditions. The study of Beams, Free and Glenn<sup>53</sup> on the absorption of galactose from the gastrointestinal tract in deficiency diseases adds further confirmation of these known facts. In patients with active pellagra and nontropical sprue there was marked impairment of galactose absorption. Curiously enough, a distinct improvement in the absorption of galactose accompanied clinical improvement in patients with pellagra but not in those with sprue. Two of 4 patients with rosacea keratitis showed decreased galactose absorption, which improved under riboflavin therapy. Any study of deficiency conditions should include a consideration of celiac disease. For this reason the work of May and McCreary<sup>54</sup> deserves mention. A deficient absorption of vitamin A is a constant feature of celiac disease, but this fact is of limited value in differentiating it from other conditions producing the celiac syndrome. The level of carotenoids in the blood of patients with celiac disease seems to follow the clinical course of the disease, being low throughout the active stage and rising with clinical improvement. The absorption of vitamin A appears to return to an entirely normal level when recovery is complete.

MacKay and Clark<sup>55</sup> showed that the rate of absorption of dextrose from the rat intestine under conditions of forced feeding depended on the amount and concentration of sugar. Variable doses administered in a fixed volume gave a relatively constant absorption coefficient, but when variable doses of dextrose were administered at the same concentration but in variable volumes, the absorption coefficient was related to the dose of dextrose. By concentrating the period of eating through a prior period of fasting or by giving dextrose alone and increasing the appetite with injections of protamine zinc insulin or by the use of a cold environment, a great increase in the absorption coefficient was obtained. Anoxia up to and including a partial pressure of oxygen equivalent to an altitude of 28,000 feet (8,400 meters), according to Northup and Van Liere,<sup>56</sup> did not significantly alter the absorption of dextrose from the small intestine of the dog, although it did exert a significant

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53. Beams, A. J.; Free, A. H., and Glenn, P. M.: The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases, *Am. J. Digest. Dis.* **8**:415, 1941.

54. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease: Interpretation of the Vitamin A Absorption Test, *J. Pediat.* **18**: 200, 1941.

55. MacKay, E. M., and Clark, W. G.: The Rate of Glucose Absorption from the Intestine of the Rat, *Am. J. Physiol.* **135**:187, 1941.

56. Northup, D. W., and Van Liere, E. J.: The Effect of Anoxia on the Absorption of Glucose and of Glycine from the Small Intestine, *Am. J. Physiol.* **134**:288, 1941.

depressing action on the absorption of aminoacetic acid. This experiment suggests that possibly an oxidative process is directly involved in the absorption of aminoacetic acid. Driver<sup>57</sup> studied the effect of hexylresorcinol and other agents on the absorption of sugars, chloride and sulfate from the alimentary tract. His results indicate that hexylresorcinol and ammonium thiocyanate inhibit the activity of carbonic anhydrase in vitro and that both lower the absorption of chloride from the alimentary tract. He believes that there is a special mechanism for at least a part of chloride absorption and that carbonic anhydrase may be involved, along with a structural arrangement favorable for the absorption of the ion. The absorption of sulfate likewise is probably partly dependent on some biologic agent. Peters<sup>58</sup> observed that the intestinal absorption of chloride, water and sulfate was appreciably diminished by the administration of bile salts, which in some instances actually produced a transfer of chloride and water toward the intestinal lumen. Werch and Ivy<sup>59</sup> concluded that a negligible amount, if any, of galacturonic acid is absorbed from either the small or the large intestine of dogs or from that of human beings.

One aspect of the absorption of undigested protein from the intestinal tract is presented by Harten, Livingston and Walzer.<sup>60</sup> Their studies have a particular bearing on the question of food allergy. A cutaneous site on a rhesus monkey was sensitized by the intracutaneous injection of human serum containing skin-sensitizing antibodies. After an interval of twenty-four to forty-eight hours to permit fixation of the antibodies at the cutaneous site, the specifically related antigen was administered orally. The lighting up of the sensitized cutaneous site with an urticarial reaction within a few minutes marked the entrance of unaltered protein into the circulation. The authors believe that experimental evidence now exists which indicates that antigens may be absorbed from any part of the intestinal tract, though the rate of absorption may vary somewhat in different organs. The amount of antigen necessary to produce the allergic reaction has been shown to be infinitesimally small. The "absorption time" of the cottonseed protein utilized in these experiments was only two minutes from the stomach,

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57. Driver, R. L.: Effects of Hexylresorcinol and Other Agents on the Absorption of Sugars, Chloride and Sulfate from the Alimentary Tract, *Am. J. Physiol.* **135**:330, 1942.

58. Peters, H. C.: The Influence of Bile Salts on Active Intestinal Absorption of Chloride, *Am. J. Physiol.* **136**:340, 1942.

59. Werch, S. C., and Ivy, A. C.: Is Galacturonic Acid Absorbed by the Small and Large Intestine? *Proc. Soc. Exper. Biol. & Med.* **48**:9, 1941.

60. Harten, M.; Livingston, S., and Walzer, M.: Studies in Absorption of Undigested Protein: IX. Absorption from the Stomach and Esophagus, *J. Lab. & Clin. Med.* **27**:56, 1941.

whereas the "absorption time" of the same protein from the esophagus was apparently ten minutes.

The relation of the  $p_H$  of intestinal contents to calcium and phosphorus utilization was studied by Jones<sup>61</sup> in rats. The data obtained tend to throw considerable doubt on the theory that an increase in intestinal acidity provides the basis by which fats beneficially influence calcification. Lard, oleic acid, and vitamin D all increased the acidity of the lower portion of the ileum and less consistently that of the cecum and the colon. All of these substances showed definite antirachitic activity. The administration of vitamin D produced the slightest lowering of  $p_H$  but at the same time was associated with the greatest antirachitic action. Intestinal  $p_H$  was increased by the addition of aluminum sulfate to a stock diet but resulted in severe rickets. The addition of dibasic sulfate to a low phosphorus rachitogenic diet protected the animals against rickets without changing the  $p_H$  of the intestinal contents, whereas lactose produced as much acidity in the intestine as did lard but did not show any antirachitic action.

Studies on the absorption of propylene glycol were made by Van Winkle.<sup>62</sup> He felt that the quantitative absorption of this substance by the digestive tract agreed in several respects with that demonstrated by other investigators previously for alcohol, phenol and iodide, except that the absorption of propylene glycol was more rapid and more complete.

An inconclusive study by Webster<sup>63</sup> on lead and arsenic absorption and excretion in man is of interest because it demonstrates the potential dangers incident to the use of lead arsenate in sprays. The observations were made on orchardists who ate varying numbers of sprayed apples daily. Analyses of samples of the fruit eaten showed a potential intake of 1 to 26 mg. of lead and 0.34 to 6.8 mg. of arsenic per person per day. Analyses of urine and stools showed that the largest part of the lead was eliminated in the feces, a finding in agreement with earlier experiments by Fairhall and Neal. In the present study the fecal output of arsenic equaled or exceeded the urinary output of arsenic in the majority of instances, although in the earlier experiments only traces of arsenic were regularly found in the feces. Two explanations were offered for this difference: (1) that the weathered spray residue may differ from pure lead arsenate in physical and chemical properties, and (2) that per-

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61. Jones, J. H.: The Relation of the  $p_H$  of Intestinal Contents to Calcium and Phosphorous Utilization, *J. Biol. Chem.* **142**:557, 1942.

62. Van Winkle, W., Jr.: Quantitative Gastro-Intestinal Absorption and Renal Excretion of Propylene Glycol, *J. Pharmacol. & Exper. Therap.* **72**:344, 1941.

63. Webster, S. H.: Lead and Arsenic Ingestion and Excretion in Man, *Pub. Health Rep.* **56**:1359, 1941.

sons having chronic exposure to compounds containing lead and arsenic may differ from persons with only acute exposure in their utilization and excretion of arsenic. Because of the frequent occurrence of such an exposure to toxic materials throughout the country, it is to be hoped that further studies will be carried out.

Absorptive experiments by Melnick, Robinson and Field<sup>64</sup> on the fate of thiamine in the digestive secretions are of interest. Optimum absorption of thiamine in part is related to the presence of food in the stomach, which permits the vitamin to be retained for a longer period in that organ, thus enabling direct absorption and avoiding subsequent destruction in the more alkaline medium occurring in the small intestine. Normal acidity of the gastric chyme reduces the  $p_H$  of secretions in the duodenum, and this in turn again decreases the possibility of the destruction of the vitamin  $B_1$  by the alkaline bile and pancreatic juice. An important corollary of the fact that thiamine is stable in normal gastric juice is that the oral administration of thiamine in conjunction with antacids is contraindicated if optimum utilization of the vitamin is desired. Studies on the absorption of thiamine from the intestine of rats have been carried out by Stockholm, Althausen and Borson.<sup>65</sup> Their observations seemed to indicate that phosphorylation does not play a dominant part in determining the rate of intestinal absorption of thiamine and that thyroxine does not have a stimulating effect on the rate of enzyme formation of the pyrophosphate ester. It would seem that the absorption of thiamine in the intestine probably takes place by means of simple diffusion and is roughly proportional to its concentration in the intestine.

#### CLINICAL ASPECTS

*Mouth.*—The incidence of chronic ulcerative lesions of the mouth has been carefully investigated in a large American clinic by Keyes,<sup>66</sup> who reports a study of 2,077 oral lesions. Of these, only 1 in 4 was benign. Of the 1,561 malignant lesions, all but 38 were squamous cell carcinomas, 1 instance of which was encountered in a boy aged 19. As a rule, the malignant lesions occurred in patients over 60 years of age in association with bad dental conditions or gingivitis or in edentulous old men who chewed tobacco or smoked a great deal. Leukoplakia commonly accompanied cancer of the buccal mucosa and was prone to occur within the cheek on the side in which the chewing tobacco was held.

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64. Melnick, D.; Robinson, W. D., and Field, H., Jr.: Fate of Thiamine in the Digestive Secretions, *J. Biol. Chem.* **138**:49, 1941.

65. Stockholm, M.; Althausen, T. L., and Borson, H. J.: Mechanism of Intestinal Absorption of Thiamin, *Proc. Soc. Exper. Biol. & Med.* **46**:387, 1941.

66. Keyes, E. L.: Chronic Ulcerative Lesions of the Mouth: Incidence of Cancer in 2077 Cases at Barnard Hospital, *Am. J. Surg.* **56**:70, 1942.

Of the benign lesions, nearly one-third consisted in degenerative or inflammatory lesions. Little attention is paid, however, in this report to the occurrence of oral lesions secondary to vitamin deficiencies. The frequency with which the last-named type of lesion may be observed is of real clinical importance, not only because adequate therapy, as a rule, is entirely successful in relieving associated symptoms, but because it commonly suggests the presence of an underlying deficiency condition which might otherwise be missed. Rosenblum and Jolliffe<sup>67</sup> present an excellent summary of the oral manifestations of vitamin deficiencies, pointing out the various primary and contributory causes of such lesions. This paper constitutes an excellent résumé of present knowledge of buccal deficiency disease and is further enhanced by illuminating comments by Mackie. Further attention to oral lesions associated with dietary deficiencies appears in an article by Chapman and Harris,<sup>68</sup> who point out the importance of such deficiencies in conditioning inflammatory processes in the mouth. In monkeys maintained on certain vitamin-deficient diets there was noted a consistent tendency to oral lesions accompanied by an increase in the fusospirochetal flora. Furthermore, such animals maintained on an adequate stock diet tended to resist artificial implants of fusospirochetal flora under the severest of test conditions.

Damianovich and Ravizzoli<sup>69</sup> add further information in an article on stomatitis aphthosa. Nicotinic acid therapy proved highly successful in the treatment of a group of children presenting this condition. Beneficial results were obtained after the first few doses of nicotinic acid, and a cure was usually accomplished in three days, with rapid epithelization of the lesions. Gingivitis proved more refractory. The suggestion that infection of the mouth with organisms other than Vincent's may be associated with nicotinic acid deficiency is also postulated by Walton and his associates.<sup>70</sup> Although such observations are by no means new, it is still not too generally recognized that avitaminosis frequently underlies the occurrence of annoying and at times serious buccal lesions.

*Esophagus.*—Passing comment is warranted on several articles on esophageal diseases, although nothing new has appeared in the literature of the past year. Clinical observations on the symptoms and signs asso-

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67. Rosenblum, L. A., and Jolliffe, N.: The Oral Manifestations of Vitamin Deficiencies, *J. A. M. A.* **117**:2245 (Dec. 27) 1941.

68. Chapman, O. D., and Harris, A. E.: Oral Lesions Associated with Dietary Deficiencies in Monkeys, *J. Infect. Dis.* **69**:7, 1941.

69. Damianovich, J., and Ravizzoli, R.: Nicotinic Acid and Stomatitis Aphthosa, *Arch. argent. de pediat.* **16**:21, 1941.

70. Walton, C. H. A.; Graham, H. M., and Lansdown, L. P.: Acute Ulcerative Stomatitis: Three Unusual Cases, *Lancet* **2**:214, 1941.

ciated with stenosis of the upper portion of the esophagus are presented in a rather interesting fashion by Camiel and Loewe.<sup>71</sup> On physical examination more than one third of a small group of patients showed definitely clubbed fingers, probably secondary to aspiration of ingesta into the trachea or the bronchial tree. The authors suggest that the appearance of pulmonary lesions, paralysis of the vocal cords or clubbed fingers in the absence of a known primary source should point strongly to the possibility of disease of the upper portion of the esophagus.

Adverse comment is warranted on a report by Mitchell<sup>72</sup> of a case of achalasia of the esophagus. In this instance the condition was satisfactorily relieved by esophagogastrostomy. No mention is made of careful bouginage, however, and it would seem reasonable to suggest that in such cases this measure should always be attempted before resorting to such a serious surgical procedure as that reported by the author. That such conservatism in therapeutics is entirely warranted is indicated by a careful record of Hara and Rosenvold.<sup>73</sup> In this instance complete cicatricial atresia of the esophagus of six years' duration was successfully treated, after a temporary gastrostomy, by peroral esophagoscopy with dilatation. Such procedure is well established and whenever possible should be the therapy of choice.

Fibrosis of the esophagus with subsequent narrowing is thoroughly discussed by Mosher<sup>74</sup> in a paper based on an examination of 100 autopsy specimens. The article is of particular interest because of the percentage of carefully examined material. The role of infection due to local or distant sources is discussed, and certain points of interest are brought out. Thrombosed veins, periesophageal abscesses and similar conditions are considered, and an explanation is offered for the so-called "spasm" of the pylorus that is noted at birth. The author cites 3 cases in which at birth both the pyloric and the cardiac end of the stomach was narrowed. Although one cannot easily accept the author's ideas of prenatal infection, the pathologic material presented is of real clinical interest. An experimental study by Strong and Smith<sup>75</sup> is of importance in this connection. Experiments were carried out on a strain of mice in which there was practically no evidence of an inflammatory, parasitic

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71. Camiel, M. R., and Loewe, L.: Syndrome of Upper Esophageal Stenosis, *Ann. Int. Med.* **15**:63, 1941.

72. Mitchell, H. E.: Achalasia of the Esophagus, with Report of a Case Relieved by Esophagogastrostomy, *Ann. Otol., Rhin. & Laryng.* **50**:662, 1941.

73. Hara, H. J., and Rosenvold, L. K.: Cicatricial Atresia of the Esophagus, *Arch. Otolaryng.* **34**:574 (Sept.) 1941.

74. Mosher, H. P.: Infection as a Cause of Fibrosis of the Esophagus, *Ann. Otol., Rhin. & Laryng.* **50**:633, 1941.

75. Strong, L. C., and Smith, G. M.: Stenosis of the Esophagus in Four Generations of Mice of the N. H. Strain, *Yale J. Biol. & Med.* **13**:489, 1941.

or neoblastic condition. Esophageal stenosis with proximal dilatation appeared several times in closely related individuals of this strain, and there seemed little doubt that a certain localized hyperplasia of the esophageal epithelium with active keratosis was probably the cause of the narrowing. These lesions were not observed at birth.

Cancer of the esophagus still presents a diagnostic and therapeutic challenge. The wisdom of more frequent and earlier esophagoscopy examination is properly stressed by Lindsay<sup>76</sup> as an early diagnostic procedure. To this suggestion should be added the fact that more than one esophagoscopy examination may be needed in some cases before biopsy material has been obtained that is adequate for diagnosis. This is due to the fact that the inflammatory involvement of the esophagus above the carcinomatous area frequently prevents adequate examination until skilful bouginage and dilatation have been performed, with resulting better exposure of the lesion. The results of surgical procedures are still unsatisfactory. An adequate summary of the present status of surgical treatment of esophageal cancer is presented by Sweet<sup>77</sup> and is of particular interest because of its complete discussion of the various methods that are at present available, including various types of gastrotomy and reconstruction operations. He states that the Beck-Jianu operation in the reconstruction of an external esophagus after resection in certain favorable cases of cancer of the esophagus has been tried in several instances, with satisfaction.

An unusual cause of esophageal obstruction is that reported by Gross and Freedman,<sup>78</sup> who record an instance of an occluding secondary carcinomatous tumor of the esophagus metastatic from clinically silent prostatic carcinoma.

*Diaphragmatic Hernia.*—Unusual manifestations of diaphragmatic hernias are recorded by Harrington<sup>79</sup> and Colmers.<sup>80</sup> In the 4 cases reported by Harrington, a complete hernial sac projected into the right thoracic cavity and, unlike most herniations on the right side, there was no history of previous trauma. In one of the 4 cases, in addition to a subcostosternal hernia, a second esophageal hiatus hernia was present. In 2 instances the hernial contents included omentum and bowel, and the

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76. Lindsay, J. R.: The Early Diagnosis of Carcinoma of the Esophagus, *Ann. Otol., Rhin. & Laryng.* **50**:675, 1941.

77. Sweet, R. H.: Gastrotomy in Cases of Carcinoma of the Esophagus, *Surg., Gynec. & Obst.* **73**:55, 1941.

78. Gross, P., and Freedman, L. J.: Obstructing Secondary Carcinoma of the Esophagus, *Am. J. Path.* **18**:361, 1942.

79. Harrington, S. W.: Subcostosternal Diaphragmatic Hernias, *Surg., Gynec. & Obst.* **73**:601, 1941.

80. Colmers, R. A.: Parasternal Diaphragmatic Hernia with Report of a Case on the Right Side, *Radiology* **37**:733, 1941.

patients presented the usual symptoms of intermittent digestive disturbances and partial intestinal obstruction. In the other 2 cases, however, only omentum was contained in the hernial sac, and in the absence of typical symptoms a preoperative diagnosis of a malignant lesion was made. Operative procedures were successful in all 4 cases. The discussion in Colmers' report is of interest particularly in relation to the time of development of a parasternal diaphragmatic hernia on the right side. Because of the late development of symptoms and histologic changes in the adjacent pulmonary tissue, the author believes that the hernia was acquired in later life.

A study of the symptoms associated with small hiatus hernias is presented by Jones,<sup>81</sup> with special reference to the clinical differences between these small lesions, frequently recognized with difficulty by the roentgenologist, and the much larger herniations recorded in the earlier literature. Unlike many writers, the author believes that extremely small hernias may in certain instances form the basis of acute symptoms, which not infrequently are almost indistinguishable from those associated with coronary heart disease. A careful statistical analysis of symptoms observed in a group of private patients with relatively small hernias forms the basis of this report. That large hernias may at times cause symptoms simulating cardiac disease has long been recognized, but as a rule the symptoms are not those of angina pectoris. The source of such symptoms in larger hernias is almost certainly associated with mediastinal displacement with cardiac embarrassment. An excellent report is that of McGinn and Spear.<sup>82</sup> These authors record a case of diaphragmatic hernia in an 81 year old woman with postmortem observations. The clinical symptoms were those of acute cor pulmonale with marked cyanosis, dyspnea and electrocardiographic abnormalities. Compression of the lungs by an increase in the amount of stomach herniating through the diaphragm caused an acute strain on the right side of the heart. The exact mechanism involved in the production of anginal symptoms by lesions of the esophagus, stomach or gallbladder is still not thoroughly understood. Numerous attempts to elucidate the problem have been recorded in the literature since von Bergman's studies in 1932. Consideration of the various possibilities are to be found in the article by Jones (*vide supra*) and in one by Andrews<sup>83</sup> on cardiovascular disturbances in gastrointestinal diseases.

81. Jones, C. M.: Hiatus Esophageal Hernia, with Special Reference to Comparison of Its Symptoms with Those of Angina Pectoris, New England J. Med. **225**:963, 1941.

82. McGinn, S., and Spear, L. M.: Diaphragmatic Hernia Presenting the Clinical Picture of Acute Cor Pulmonale, New England J. Med. **224**:1014, 1941.

83. Andrews, C. L.: Cardiovascular Disturbances in Gastrointestinal Diseases, J. M. Soc. New Jersey **38**:305, 1941.



*Gastritis and Gastroscopy.*—As was to be expected since the introduction of the flexible gastroscope, the number of articles devoted to a consideration of gastritis and allied conditions has steadily increased. Much of the literature is still inconclusive or contradictory, but there is evidence of a widespread and earnest attempt completely to reevaluate the clinical and the experimental use of gastroscopy and the true clinical significance of gastritis.

Pathologic changes occurring in nutritional gastritis in rats are recorded by Berg.<sup>84</sup> The observations were carefully controlled, and it was found that in those animals placed on inadequate diets, gastritis could be produced in a relatively short time, with involvement of the antrum and the rumen separately or together. The pathologic changes in the mucosa of the antrum and those in the mucosa of the rumen were essentially similar and consisted in ulcerations in areas of epithelial hyperplasia that tended to undergo spontaneous healing. Recurrent necrosis and hemorrhage appeared to develop in healing defects and to lead to chronic changes. The fundus was relatively free of lesions, but those noted were essentially hemorrhagic erosions. Although such changes cannot be compared with certainty to those observed in deficiency disease in human beings, they should cause serious consideration as regards some of the potential factors in the causation of gastritis.

One of the obvious needs in a study of clinical gastritis as observed gastroscopically at the present time is a correlation between the gastroscopic findings and the results of histologic examination of biopsy specimens of the stomach obtained either at operation or at gastroscopy. Such studies are beginning to appear. Swalm and Morrison<sup>85</sup> compared gastroscopic and histologic observations of the stomach in patients with gastric and with extragastric disease during life and at autopsy and found that there was agreement between the two in about half of a small series of cases. In one fourth of the cases there was complete disagreement, and in a similar number there was only questionable conformity. These authors conclude that the gastroscopic appearance of severe gastritis is usually verified by histologic examination, but they point out the important fact that the gastroscopic appearance of a mild or moderate degree of gastritis or of a normal stomach may be contradicted by the histologic examination of a biopsy specimen. A somewhat similar study on a slightly larger group has recently been carried out by

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84. Berg, B. N.: Pathological Changes in Nutritional Gastritis in Rats, *Am. J. Path.* 18:49, 1942.

85. Swalm, W. A., and Morrison, L. M.: Gastroscopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease During Life and at Autopsy, *Am. J. Digest. Dis.* 8:391, 1941.

Benedict and Mallory,<sup>86</sup> in which specimens of stomach obtained at the time of gastric resection were subjected to careful microscopic investigation and the findings compared with the initial gastroscopic diagnoses. As in the work done by Swalm and Morrison, a good correlation was observed in those cases in which definite gastritis by gastroscopy was shown, but a definite lack of correlation was observed in some important instances. As a rule, it is probably safe to conclude that gross gastric changes noted by experienced gastroscopists will be found to correspond fairly closely to histologic changes typical of the various forms of gastritis. It is obvious, however, that minor changes in the gastroscopic picture must be classified with great care, and it is particularly important that such changes are not overemphasized in order to explain symptoms and to form the basis of therapy.

It is still essential to indicate the necessity for continued skepticism in order to arrive at a rational conclusion as to the clinical importance of gastritis as diagnosed by gastroscopy. Howard and Martin<sup>87</sup> stress such a point of view in a careful review of the gastritis problem and refer to Schindler's statement that only about one fifth of the stomachs examined by him are normal, which probably tends to overemphasize greatly the actual incidence of true gastritis. They, like Ruffin and others, correctly urge the accumulation of further data before final conclusions are attempted regarding the incidence or morbidity of various forms of gastritis. They stress the need for adequate gastroscopic studies on psychoneurotic subjects, with or without gastric symptoms. Such a suggestion is of prime importance, and one must again refer to the original observations recorded by Beaumont on the striking changes in the gastric mucosa following emotional upsets and to the recent experiments made by Wolff and Wolf.<sup>2</sup> In my opinion it would seem highly probable that profound and fairly lasting mucosal changes could be observed during acute or more prolonged states of emotional tension which could easily mimic many of the changes now diagnosed as being due to gastritis. Such a concept is stressed, for example, by Kutschera-Aichbergen<sup>88</sup> in an excellent review of the problem. In common with other writers he indicates the important fact that frequently gastroscopic changes are demonstrated which may in no way be associated with

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86. Benedict, E. B., and Mallory, T. B.: Correlation of Gastroscopic and Pathologic Findings in Gastritis, read before the Section on Gastro-Enterology and Proctology, American Medical Association, Atlantic City, N. J., June 12, 1942.

87. Howard, J. T., and Martin, L.: The Gastritis Problem, *South. M. J.* 34:921, 1941.

88. Kutschera-Aichbergen, H.: Remarks on Gastritis, *Wien. klin. Wchnschr.* 54:335, 1941.

clinical symptoms and which, therefore, must be carefully evaluated before initiating an intricate and frequently expensive course of treatment and one which, in addition, may be ill advised.

In an attempt to estimate the symptomatology incident to various forms of gastritis, McClure, Sweetsir and Jankelson<sup>89</sup> make certain interesting points. Of 68 patients showing hypertrophic or atrophic gastritis, in nearly two-fifths the associated symptoms could be attributed to a coexisting ulcer or cholecystic disease. In the remainder mild or severe epigastric discomfort was noted. Unlike the experience recorded by many observers, these authors state that the epigastric pain was invariably related to the time of taking food and was relieved by the ingestion of food or alkali. In the absence of peptic ulcer such a manifestation of symptoms is certainly unusual, to say the least, and is not to be taken as characteristic. The frequent occurrence of fatigue noted by these authors in association with the atrophic type of gastritis is of interest and would certainly raise the suspicion of associated nutritional disturbances, possibly in relation to true deficiency disease.

A further investigation of the significance of achlorhydria with particular reference to gastroscopic observations has been made by Carey and his associates.<sup>90</sup> Although the authors are careful not to draw conclusions, their observations on a large group of patients (233 patients with gastric achlorhydria) are of extreme interest. Perusal of the article would seem to justify the suggestion that the term atrophic gastritis is frequently a misnomer, inasmuch as it implies an inflammatory process rather than a degenerative one or one incident to a generalized deficiency state. In a large number of Carey's patients various manifestations of deficiency disease were carefully noted, and it is highly probable that the gastric changes were simply reflections of a general underlying condition. Extremely careful observations were made on a group of patients with pernicious anemia, and it was noted that the mucosal atrophy was in the body of the stomach and that the antral region was not perceptibly involved. Although the authors state that this is not consistent with Meulengracht's work on the "pyloric gland organ," reference to Fox and Castle's recent article<sup>48</sup> would indicate that not only are the observations entirely correct but they fit in with a proper concept of the expected site of the lesion in pernicious anemia in human beings, Meulengracht's work being based on observations made on the hog stomach. These authors, in company with others already cited, feel that the subject of gastritis has to be further investigated to obtain a com-

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89. McClure, C. W.; Sweetsir, F. N., and Jankelson, I. R.: Chronic Gastritis: Gastroscopic and Clinical Study, *New England J. Med.* **225**:259, 1941.

90. Carey, J. B.; Wetherby, M., and Ylvisaker, R. S.: Gastric Observations in Achlorhydria, *Am. J. Digest. Dis.* **8**:401, 1941.

plete correlation between gastroscopic data, histologic data on resected or biopsy material and clinical evidence of disease.

The role of chronic alcoholism in the production of chronic gastritis is still in the realm of speculation. As Berry<sup>91</sup> points out, evidence from the literature on attempts to produce chronic alcoholic gastritis is inconclusive. Pathologists have not supplied any evidence in the literature of unequivocal chronic gastritis due to alcohol. Berry cites one well controlled observation made by Hirsch in 1916 who demonstrated frequent gross and microscopic petechiae or ecchymotic hemorrhages but no true inflammatory reaction. No previous gastroscopic study of alcoholic addicts has appeared in the American literature. In the author's opinion, in the one report in the foreign literature, on 45 patients, the extensive atrophic gastritis described was probably not due to alcohol directly. Berry carried out gastroscopic studies on 100 patients with unquestionable chronic alcoholism. All were ambulatory, and none had an enlarged or painful liver or ascites. Sixteen came to the clinic because of some type of digestive distress, while the remaining 84 did not seek medical help but were induced to come to the clinic for this study. In this group of patients, one-third showed no evidence of gastritis, a second third showed mild chronic superficial gastritis and a final third showed unequivocal chronic gastritis. These observations are timely and certainly present substantial evidence that chronic alcoholism may be associated with chronic inflammatory changes in the gastric mucosa. Although the observations are of extreme interest, they still fail to prove the point, however, as to the cause of the condition. It may well be that, as in cirrhosis, one must carefully differentiate between cause and associated factors. It is entirely within the realm of possibility that in persons chronically addicted to alcohol, changes in the gastric mucosa develop partly because of the stimulating or irritating effect of alcohol and partly because of associated dietary indiscretions, or more probably, deficiencies based on the substitution of alcohol for food. The subject is still *sub judice* and will warrant further careful observations. In spite of failure to present absolute proof of the etiologic role played by alcohol in the production of chronic gastritis, there can be little doubt from these observations and clinical experiences that chronic addiction to alcohol carries in its train serious consequences, among which is the frequent occurrence of chronic gastric disease. An entirely comparable report on an equal number of subjects is presented by Gray and

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91. Berry, L. H.: Chronic Alcoholic Gastritis: Evaluation of the Concept, with Gastroscopic Studies in One Hundred Cases, J. A. M. A. **117**:2233 (Dec. 27) 1941.

Schindler.<sup>92</sup> The 100 men who were examined had consumed an average of 2.8 pints (1.3 liters) of alcohol daily for more than twenty years, yet gastroscopic examination revealed that approximately half the subjects did not give evidence of any important gastric abnormalities. In 45 per cent the gastric alterations consisted merely in superficial gastritis, atrophic gastritis or a combination of the two. Gastrointestinal complaints occurred in about two thirds of those showing severe grades of gastritis, whereas only 7 per cent of the addicts with normal-appearing stomachs experienced "indigestion." No correlation was observed between the incidence and severity of gastritis and the duration of alcoholism, the amount of alcohol consumed, the abuse of nicotine, dental infection or vitamin deficiencies. It is obvious that the question is still open.

Certain unusual gastroscopic observations are worthy of mention. Einsel<sup>93</sup> reports a case of superficial ulcerative gastritis following heavy antisyphilitic therapy. Because of gastric distress and nausea triparsamide treatment was stopped, and two weeks later roentgen and gastroscopic examination showed superficial erosions of the gastric mucosa. Seven months later a second gastroscopic examination revealed that the gastric mucosa was entirely normal, except for some possible transient changes secondary to the recent administration of acetylsalicylic acid.

It is not surprising that advanced pulmonary tuberculosis may be associated with various gastrointestinal abnormalities. Hardt and his associates<sup>94</sup> made a gastroscopic study of 150 patients with late pulmonary disease due to tubercle bacilli. Approximately one-third showed atrophic changes similar to those classified as atrophic gastritis, and in addition, at times there was a coincidence of superficial lesions with marked hyperemia and mucosal edema, as well as evidence of local atrophy. The authors conclude, probably correctly, that the hyperemic, edematous stage represents an earlier lesion. In all probability, the gastritis is non-specific as far as tuberculosis is concerned, but it is unfortunate that no associated histologic studies were performed.

That gastritis alone may be the sole cause of serious or even fatal hemorrhage is now firmly established. A further report on this particular aspect of the problem of gastritis is presented by Benedict.<sup>95</sup> It

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92. Gray, S., and Schindler, R.: The Gastric Mucosa of Chronic Alcoholic Addicts: A Gastroscopic Study, *J. A. M. A.* **117**:1005 (Sept. 20) 1941.

93. Einsel, I. H.: Superficial Ulcerative Gastritis Following Triparsamide Therapy for Syphilis, *Am. J. Digest. Dis.* **9**:191, 1942.

94. Hardt, L. L.; Weisman, M., and Coulter, J. S.: Gastric Atrophy in Advanced Pulmonary Tuberculosis, *Proc. Inst. Med. Chicago* **13**:418, 1941.

95. Benedict, E. B.: Hemorrhage from Gastritis: A Report Based on Pathological, Clinical, Roentgenological and Gastroscopic Findings, *Am. J. Roentgenol.* **47**:254, 1942.

includes proof from autopsy and from surgical material, as well as from numerous gastroscopies, in over 200 cases of gastritis studied during a particular period. Bleeding occurred in one fifth of the cases, irrespective of the type of gastritis. Study of an additional group of cases of ulcer yielded data in keeping with those presented by other observers, that at times gross hemorrhage may occur from the associated gastritis rather than from the local ulcer. It is of interest that careful roentgen examination suggested gastritis in only 20 per cent of the cases in which gross hemorrhage was due to gastritis alone.

The cause for the divergence between the roentgen and the gastroscopic diagnosis of gastritis is well expressed by Berridge.<sup>96</sup> He rightly points out that the roentgenologist examines the gastric mucosa in a definite state, that of resting relief, whereas the gastroscopist employs an inconstant amount of distention. The article bears the imprint of a certain amount of defense reaction but is nevertheless of interest. The supplementary roles of the roentgenologist and the gastroscopist are well outlined by Davidson and Rose,<sup>97</sup> who compare the respective data from 600 gastroscopic investigations, 226 of which were checked by roentgen examination. According to these authors, roentgen investigation may give more information than gastroscopy in the following conditions: lesions on the lesser curvature of the pyloric antrum; estimation of the size of an antral cancer; lesions on the greater curvature, and lesions in the distal pouch of an hourglass stomach. Per contra, they point out that the early and accurate recognition of primary neoplasm in gastric ulcer belongs to the field of gastroscopy. Such an article is reasonably critical of the two fields of investigation and provides a basis for adequate and advantageous cooperation between the services involved.

It is still unfortunately true that adequate gastroscopic examination is frequently missing in cases in which the presence of a neoplastic lesion of the stomach has been suspected but not proved by roentgen examination. This is well illustrated in an article by Myhre,<sup>98</sup> who presents an adequate description of the significance of large niches in the stomach. In 23 instances surgical exploration had followed the roentgen examination, but it is of interest to note that of the large craters encountered in the 23 patients, only 9 were due to carcinoma and the other 14 were associated with benign ulcers. The average diameter of the benign niches was around 4 cm., in 1 individual case an ulcer crater 6.5 cm. in diameter

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96. Berridge, F. R.: The Radiological Aspects of Gastritis, *Brit. J. Radiol.* **15**:1, 1942.

97. Davidson, S. W., and Rose, J. D.: The Value of Cooperation Between the Radiologist and the Gastroscopist, *Brit. J. Radiol.* **14**:307, 1941.

98. Myhre, H.: Significance of Large Niches in Stomach, *Acta radiol.* **22**:482, 1941.

being noted. Those patients with malignant disease did not show any greater size of the craters. Such findings are important in demonstrating the need for accurate examination by an experienced gastroscopist as a supplement to careful roentgen study. There is little doubt that many of these operations could have been properly avoided and the gastric lesions permitted to heal under medical therapy had gastroscopy been performed. Obviously, the gastroscopist cannot always be the final arbiter in this difficult question, but in most instances, repeated careful observations will provide the necessary information in differentiating between a benign and a malignant lesion.

Schindler<sup>99</sup> contributes another careful series of observations on the appearance of the gastric mucosa in the presence of benign adenomas of the stomach. Thirty-six adenomatous polyps were observed in the course of 2,167 consecutive gastroscopies. The finding of associated atrophic gastritis occurred with sufficient frequency to lead him to the conclusion that an atrophic gastric mucosa has a seven times greater predisposition to the formation of such tumors than has a normal gastric mucosa. Here again, such a definite statement must be scrutinized rather carefully in the light of subsequent examinations, but the observation is important and cannot be dismissed.

The rarity of multiple polyps of the stomach is evidenced in a report by Giere.<sup>100</sup> In a review of over 34,000 autopsies at the University of Minnesota only 32 instances were encountered. He cites Stewart as reporting only 20 cases of multiple polyps in 11,000 autopsies, at the Leeds General Infirmary, and Carmen as encountering only 2 instances in 50,000 roentgen examinations of the stomach. The author reports 1 case, which again illustrates the importance of the correlation between gastroscopic and roentgen examination. In this particular case gastroscopy confirmed the roentgen evidence of polyps but gave additional information in that it disclosed the presence of polyps not seen on roentgen examination, as well as erosions and evidence of atrophic gastritis.

A rather interesting study is that made by Usher,<sup>101</sup> who reports gastroscopic observations on 19 patients suffering from varying degrees of rosacea, with control studies on 15 patients with other types of dermatoses. Gastritis of varying degrees of severity was present in all except 1 of the patients with rosacea, while of the patients with dermatoses of

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99. Schindler, R.: The Gastric Mucosa in Benign Adenomas, *Am. J. Digest. Dis.* **9**:149, 1942.

100. Giere, C. N.: Gastric Polyposis: Case Observed Gastroscoically, *South. M. J.* **34**:927, 1941.

101. Usher, B.: Gastroscopic Observations in Rosacea, *Arch. Dermat. & Syph.* **44**:251 (Aug.) 1941.

varying types, only 4 showed any evidence of gastric alterations. No constant type of gastritis was noted in the patients with rosacea. Repeated gastroscopic investigations in 2 patients during the course of treatment showed coincidental improvement both in the gastritis and in the rosacea, which is further evidence of the probable influence of deficiency conditions in causing gross gastric abnormalities.

To those actually performing gastroscopies a modification of the Wolff-Schindler gastroscope reported by Taylor<sup>102</sup> may be of interest. One possible advantage of the instrument described is that the flexibility is controlled and, if desired, the instrument can be made completely flaccid.

The report by Schiff and Shapiro<sup>103</sup> on perforation of the stomach during the use of the flexible gastroscope is important for two reasons: First, it illustrates the potential hazard attaching to the use of the gastroscope, and second, it emphasizes the extreme infrequency with which such accidents occur. It is important to note that there was no pain at the actual time of perforation, but the appearance of blood covering the instrument at once suggested what had occurred, and the subsequent appearance of abdominal "spasms" led to a correct diagnosis. Schindler has previously pointed out that the diagnosis of perforation of the stomach at gastroscopy may be made prior to the onset of pain if the stomach remains collapsed in spite of air inflation. A still more unusual accident secondary to gastroscopy is that described by Touroff,<sup>104</sup> who reports a perforation of the cervical portion of the esophagus, due apparently to the dislodging of the flexible rubber bougie at the distal end of the apparatus. In this instance, the appearance of a small amount of blood in the patient's mouth caused withdrawal of the instrument, which had been passed only about 6 inches (15 cm.) beyond the upper incisors, and it was noted on withdrawal that the rubber bougie was missing. Within a few minutes the patient complained of pain over the right side of the neck, and subsequent examination at operation revealed perforation of the esophagus and the foreign body lying free in the periesophageal tissue. Prompt operation resulted in a perfect recovery. Although the possibility of such serious accidents should not be overlooked, their rarity is disclosed in the results of a recent questionnaire circulated by Schindler (1940), which showed that only 10 serious accidents had occurred in a total of over 22,000 gastroscopic examinations.

102. Taylor, H.: A New Gastroscope with Controllable Flexibility, *Lancet* 2:276, 1941.

103. Schiff, L., and Shapiro, N.: Perforation of the Stomach with the Flexible Gastroscope: Case Report, *Am. J. Digest. Dis.* 8:260, 1941.

104. Touroff, A. S. W.: Perforation of the Cervical Esophagus with the Flexible Gastroscope, *Ann. Surg.* 114:369, 1941.



*Peptic Ulcer.*—The ulcer problem continues to attract a proper amount of attention, both from the experimental side and from various therapeutic angles. Among other researches attempting to throw light on the causation of this troublesome condition the work of Necheles and Olson<sup>105</sup> should be mentioned. These authors carried out an experimental investigation of gastrointestinal secretions and motility following burns and their relation to ulcer. The results of severe burns were studied in a series of dogs under anesthesia. Salivary, biliary and pancreatic secretions were practically always diminished. In general, the volume of gastric secretion and the degree of acidity increased, and in 1 animal studied a prepyloric ulcer was encountered. The increased volume of gastric secretion seemed to depend in part on infusions, and the increased acidity appeared to be related to the effect of infusions plus previous feeding. After peripheral burns a considerable increase in intra-abdominal pressure and gastric motility was observed. The change in gastric motility was particularly marked in the pyloric antrum and began immediately after a burn had been produced. This increase in motor activity was not altered by bilateral section of the splanchnic nerves or of the vagi or of both. In fact, vagal section seemed to enhance the gastric motor response to a burn, but the intravenous injection of atropine abolished the hypermotility. The relation of these results to Curling's ulcer are fully discussed by the authors, who undoubtedly have contributed some important information to the causation of at least one type of peptic ulcer.

The effect of local vascular changes in the stomach and the duodenum in relation to the ulcer problem has been approached by Berg,<sup>106</sup> who in normal and in vagotomized dogs was able to produce motor abnormalities and scattered superficial gastric erosions after a single injection of pitressin. With frequent injections gastric lesions were induced in normal and in vagotomized animals, particularly in the latter. The lesions were extensive, and acute and hemorrhagic duodenitis was also encountered. In sympathectomized animals gastric lesions were not obtained. Microscopically, some of the ulcerated areas extended down to the muscularis. The performance of vagotomy and sympathectomy without the use of pitressin did not result in ulcerating lesions. The relation between such results and peptic ulcer in human beings is, of course, inferential, but there can be no doubt that various factors which

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105. Necheles, H., and Olson, W. H.: Experimental Investigation of Gastrointestinal Secretions and Motility Following Burns and Their Relation to Ulcer. *Surgery* **11**:751, 1942.

106. Berg, M.: Experimental Peptic Ulcerations by Vasomotor Episodes (Pitressin Episodes) and Autonomic Disturbances, *Arch. Path.* **33**:636 (May) 1942.

in human beings produce transient or prolonged alterations in the muscular and the vascular activity of the stomach may well underlie the production and recurrence of peptic ulcer. It is highly probable that numerous factors play a role, including those that are neurogenic or hormonal in origin.

In observations on cinchophen ulcer produced in dogs Slutzky, Wilhelmj and Stoner<sup>107</sup> administered chorionic gonadotropin and posterior pituitary extract to two separate groups of animals. All the animals died from perforation of the ulcer resulting in peritonitis. There was no evidence of healing. It is of interest, however, that those animals treated with posterior pituitary extract revealed a marked inhibition of gastric acid secretion. These animals probably survived somewhat longer than the others, but the action of the pituitary extract did not prevent the occurrence of gastric ulceration and was probably an indirect action secondary to vasoconstriction.

The contribution of gastric acid to the formation of ulcer in the jejunum and the duodenum has long been recognized, although the exact mode of its activity is still not fully understood. Schiffrin and Warren<sup>108</sup> obtained what would seem to be an entirely logical series of results in cats in which various segments of the small bowel were perfused with solutions of hydrochloric acid alone and hydrochloric acid combined with pepsin. Severe ulceration resulted, and it was found that the threshold of peptic activity necessary for ulceration of the jejunum was within the range of that in normal canine gastric juice. Maximum ulceration occurred with pepsin when it was employed in a medium having a  $p_H$  within the optimum range for peptic digestion. The experiments throw no light on whether the proteolytic activity of gastric juice is an etiologic factor or an accessory factor in the production of peptic ulcer in human beings.

Recent advances in knowledge of the hormonal control of gastric secretion have already been discussed. The possible therapeutic value of a gastric secretory depressant occurring in the urine of certain persons has been studied by Sandweiss and his collaborators.<sup>109</sup> The urine of pregnant women and of normal nonpregnant women has been found to contain a principle capable of benefiting Mann-Williamson ulcers in dogs.

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107. Slutzky, B.; Wilhelmj, C. M., and Stoner, M.: The Effect of Antuitrin-S and Posterior Pituitary Extract on Cinchophen Ulcer in Dogs, *Am. J. Digest. Dis.* 8:469, 1941.

108. Schiffrin, M. J., and Warren, A. A.: Some Factors Concerned in the Production of Experimental Ulceration of the Gastro-Intestinal Tract in Cats, *Am. J. Digest. Dis.* 9:205, 1942.

109. Sandweiss, D. J.; Sugarman, M. H.; Friedman, M. H. F.; Saltzstein, H. C., and Farbman, A. A.: The Effect of Urine Extract on Peptic Ulcer: An Experimental and Clinical Study, *Am. J. Digest. Dis.* 8:371, 1941.

Experiments with extracts derived from the urine of normal men are incomplete. The urine of patients with ulcer contains much less of this inhibitory principle, and when an extract was administered in small doses, as has been already noted in animals, it produced a negligible inhibitory effect on gastric secretion, but in Mann-Williamson dogs it appeared to influence healing in some manner through stimulation of fibroblastic and epithelial proliferation and the formation of new blood vessels. With the extract at present available, it was found that when small doses were given intravenously or large doses administered subcutaneously, inhibition of gastric secretion was obtained. Sandweiss has demonstrated that subcutaneous injection of large doses of urine extract in patients with duodenal ulcer tends to inhibit the volume of gastric secretion and the total output of free acid after stimulation with histamine. The concentration of free acid was unaffected. Although the author hesitates to draw premature conclusions, it appears from the studies that urine extract therapy gave encouraging results in a series of 63 patients with chronic duodenal ulcer. It did not prevent recurrences, but he felt that a higher percentage of remissions resulted during treatment with the urine extract than was obtained with the usual dietary regimens or with other parenterally administered products. As has been evident in all his previous publications, Sandweiss is extremely conservative in attempting to evaluate the results of parenteral therapy, but from his observations it would seem reasonable to hope that a combination of the usual orthodox therapeutic measures plus urine extract therapy may produce more encouraging and more lasting results in the treatment of peptic ulcer.

Indirect evidence of an altered response in patients with ulcer to the normal inhibition of gastric acidity following the entrance of acid chyme into the duodenum is obtained from the studies of Shay and his collaborators.<sup>110</sup> In normal persons they demonstrated a depression of gastric acid secretion following the instillation into the duodenum of optimal amounts of free hydrochloric acid. Similar studies carried out in patients with duodenal ulcer after the intraduodenal instillation of even greater amounts of acid failed to elicit a normal inhibitory response in regard to gastric secretion. Such results would seem to be additional confirmation of the mode of action of enterogastrone or some similar substance.

An interesting note on the incidence of peptic ulceration is to be found in the report by Gordon and Manning,<sup>111</sup> who examined the

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110. Shay, H.; Gershon-Cohen, J.; Fels, S. S., and Siplet, H.: A Self-Regulatory Duodenal Mechanism for Gastric Acid Control and an Explanation for the Pathologic Gastric Physiology in Uncomplicated Duodenal Ulcer, *Am. J. Digest. Dis.* 9:124, 1942.

111. Gordon, J. S., Jr., and Manning, J. J.: An Autopsy Survey of Gastro-Duodenal Ulcers in Philadelphia General Hospital 1920-1937, *Am. J. M. Sc.* 202:423, 1941.

results of nearly 30,000 autopsies performed in the Philadelphia General Hospital over a seventeen year period. In this series peptic ulceration was encountered in 548 autopsies or 2.75 per cent, with no racial difference in incidence between white persons and Negroes. Males showed ulcerations only twice as frequently as females. Peaks in the incidence of the lesions appeared to be in the fifth and the seventh decade. Such a finding is of interest, though taken by itself it is difficult to interpret, inasmuch as it may not reflect the clinical incidence of ulcer in living patients. For comparative purposes the report by McMullen<sup>112</sup> should be added. Of a total of 4,400 patients subjected to roentgen examination of the gastrointestinal tract, 20 per cent were found to have peptic ulcer. As might have been predicted, duodenal ulcer occurred about four times as often as gastric ulcer and was slightly more common in men than in women. In this group of patients the peaks of incidence of gastric and of duodenal ulcer among women occurred in the fifth and the fourth decade, respectively, and similarly, the greatest incidence of gastric and of duodenal ulcer among men occurred in the sixth and the fifth decade, respectively.

Duodenal ulcer in children is undoubtedly overlooked because of its infrequent occurrence. A relatively small number of authenticated cases of ulcer in the early years of life have been reported in the literature. In recent years the diagnosis has been somewhat more frequently established, and the report of Willingham<sup>113</sup> is worthy of comment. In this instance, duodenal ulcer was eventually recognized in a 6 year old boy, for whom this diagnosis had not been considered until he vomited blood. The author correctly points out the need for more careful roentgen investigation of gastrointestinal complaints in children. Bird, Limper and Mayer<sup>114</sup> in a review of the literature noted 118 cases in which operations were performed for peptic ulceration in infants and children. They report 1 case in which operation was performed within thirty-four and a half hours after birth for a perforated duodenal ulcer, with a satisfactory outcome.

Because of the frequency with which digestive symptoms occur in the presence of heart disease, Walsh and his collaborators<sup>115</sup> made a statis-

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112. McMullen, J. W.: A Roentgenographic Study of the Relative Incidence of Gastric and Duodenal Ulcer, *Radiology* **37**:194, 1941.

113. Willingham, T. I.: Duodenal Ulcer in Children: Report of Case, *J. M. A. Georgia* **30**:271, 1941.

114. Bird, C. E.; Limper, M. A., and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children, *Ann. Surg.* **114**: 526, 1941.

115. Walsh, B. J.; Bland, E. F.; Taquini, A. C., and White, P. D.: Association of Gallbladder Disease and of Peptic Ulcer with Coronary Disease, *Am. Heart J.* **21**:689, 1941.

tical study of the necropsy protocols of a large group of patients who died at the age of 20 or more years. Of 2,737 patients, nearly one fifth had atherosclerosis of the coronary vessels and one sixth of the entire group showed structurally abnormal gallbladders. There were 122 instances of coronary disease and disease of the gallbladder occurring in the same person. Peptic ulceration was encountered in a little over 5 per cent of patients. It was evident from the protocols that disease of the gallbladder occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries, but there was no evidence of any similar association between arterial disease and peptic ulceration. The last-named association is probably coincidental. In this connection a comment is warranted on the report by Hochrein and Schleicher,<sup>116</sup> who believe that there is a close relation between peptic ulcer and coronary insufficiency. These authors have attempted to prove their point on the basis of clinical impressions and electrocardiographic studies on 100 patients with ulcer and with or without symptoms of cardiac disease. The studies are far from convincing, however, and are not borne out by the statistical data presented in the preceding paper. Neurocirculatory disturbances are certainly not uncommon in patients with ulcer, and it should be pointed out at the same time that by far the great majority of patients with ulcer have a tendency toward hypotension, rather than hypertension, and in my opinion, have relatively few symptoms suggestive of coronary heart disease. Hochrein and Schleicher illustrate their point by referring to the gastroduodenal disturbances frequently associated with hiatus hernia, a condition in no way comparable to ulcer inasmuch as it occurs in an entirely different type of person, in whom cholelithiasis and changes in the coronary arteries are common. The article is quite unconvincing but is of interest because of the questions that it raises, particularly in relation to the similarity between symptoms arising from cardiovascular disease and those due to disturbances in the digestive tract.

It has previously been pointed out (Blackford and others) that atypical histories of ulcer occur with sufficient frequency to warrant serious consideration in cases of doubtful disease of the digestive tract. Of equal importance is the fact that occasionally patients with ulcer may have absolutely no symptoms until serious accidents occur, such as perforation or hemorrhage. Norfleet<sup>117</sup> comments on such an occurrence, citing individual cases, and in this regard it is pertinent to mention that

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116. Hochrein, M., and Schleicher, I.: *Peptic Ulcer and Angina Pectoris*, München. med. Wchnschr. 88:328, 1941.

117. Norfleet, W. J.: *Peptic Ulcers, with Special Reference to Non-Symptomatic Type and Case Reports of Rupture into Peritoneal Cavity and Intestinal Hemorrhage*, New Orleans M. & S. J. 94:183, 1941.

evidence is accumulating that a higher threshold of pain may be a not uncommon phenomenon in patients with ulcer. A duodenal ulcer, for example, may be activated and may progress rapidly without the patient being aware of painful or uncomfortable sensations, thereby clouding the diagnosis or postponing a diagnosis until a serious complication occurs.

Therapeutic measures directed toward the healing of ulcer present little modification over those noted in previous years, except for the as yet untried benefits of preparations of urogastrone or enterogastrone. Antacid therapy still occupies an important place in the literature, and it is of interest to note the insistence on the various means of obtaining control of gastric hyperacidity that are still advocated. Smith,<sup>118</sup> for example, believes that continuous intragastric drip provides the only means of constantly maintaining a low acid level with the use of milk and (or) aluminum hydroxide. The mechanical difficulties encountered in the use of aluminum hydroxide drip therapy are noted by Drumheller,<sup>119</sup> who has devised a rather complicated mechanical means of insuring a constant steady flow of this bland material. The principles of tube therapy are far from new, although the material introduced into the drip apparatus have been modified from time to time. Secher<sup>120</sup> is another warm advocate of an inlying tube for the treatment of peptic ulcer, using a mixture of various bland foods to maintain a good state of nutrition. The results, however, would seem to be no better than those obtained by simpler methods, and it would seem that in many instances the annoyance of an inlying tube could be avoided without prolongation of the hospital stay for patients with ulcer or without unsatisfactory end results as far as healing is concerned. It would seem that the indications for tube therapy are few and that it should be employed only in selected cases in which other simpler methods have failed to be effective.

Compounds containing bismuth have been used intermittently for years in the treatment of gastric disease, and the report of Alstead<sup>121</sup> is therefore of interest. He believes that in therapeutic doses bismuth carbonate offers little protection to the gastric mucosa and frequently tends to collect in dependent portions without actually protecting the ulcerating areas. He concludes that in gastrointestinal disease bismuth carbonate is no more valuable than powdered milk or lactose in the relief of pain.

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118. Smith, W. E.: The Control of Gastric Hyperacidity in Peptic Ulcer, *Brit. M. J.* **2**:13, 1941.

119. Drumheller, G. H.: Problems Encountered in the Use of Aluminum Hydroxide Gel by Naso-Gastric Drip in the Treatment of Peptic Ulcer, *Am. J. Digest. Dis.* **8**:443, 1941.

120. Secher, K.: Tube Treatment of Chronic Gastric and Duodenal Ulcers, *Acta med. Scandinav.* **106**:1, 1941.

121. Alstead, S.: Action of Bismuth Carbonate in Gastric Disease, *Lancet* **2**:420, 1941.

The troubled question of alkalosis complicating alkali therapy of peptic ulcer is thoroughly studied by Kirsner and Palmer,<sup>122</sup> who are consistent and enthusiastic advocates of this form of therapy. The occurrence of alkalosis on one or more occasions in 111 patients with peptic ulcer treated by the Sippy regimen is carefully analyzed, and the symptomatology and chemical changes noted. Alkalosis was not a direct function of the quantity of alkali received, and there was no constant relation between the severity of symptoms and the degree of chemical alkalosis. It is of some interest that bleeding occurred in 60 of 135 episodes of alkalosis, but there seemed to be no correlation between the frequency of alkalosis and the severity of the bleeding. Such a high frequency of hemorrhage in alkalotic episodes suggests the possibility that sudden massive loss of blood may be associated with an alteration in renal blood flow sufficient to be an important factor in the production of alkalosis. Disease of the genitourinary tract was demonstrated in only 16 patients. Another precipitating factor suggested by the authors was excessive loss of gastric juice, either by vomiting or by therapeutic aspiration. The important fact is noted that it was not necessary to discontinue alkali therapy or to administer additional chloride in 51 of the 135 episodes. In the remaining episodes, however, treatment was modified by a change in the antacid employed, by discontinuance of the alkali or by parenteral administration of fluids and sodium chloride. The effect of prolonged alkali therapy on renal function was studied in half the patients, and it was observed that renal function was not permanently decreased by prolonged administration of alkali. Such a study is of value because of the completeness with which this particular phase of antacid therapy is reviewed. Whether antacids are necessary in the successful handling of most peptic ulcers is still a matter of individual experience and opinion, although there can be no doubt that such treatment represents a valuable and most important contribution to the effective management of many ulcer problems. The successful treatment of peptic ulcer without alkalis is discussed by Dick and Eisele,<sup>123</sup> who report their experiences in the treatment of patients with ulcer by simply dietary measures. Such a report contributes nothing new but is of importance because it indicates the efficacy of the simplest method of treatment and one which is so frequently successful in dealing with this condition.

The diagnosis of bleeding from peptic ulcer is frequently missed because of failure to perform simple stool examinations. It is of importance to note that a daily loss of blood from the upper portion of the intestinal tract of as little as approximately 10 cc. may result in positive

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122. Kirsner, J. B., and Palmer, W. L.: Alkalosis Complicating the Sippy Treatment of Peptic Ulcer, *Arch. Int. Med.* **69**:789 (May) 1942.

123. Dick, G. F., and Eisele, C. W.: The Treatment of Peptic Ulcer Without Alkalis, *J. A. M. A.* **118**:38 (Jan. 3) 1942.

results of tests for occult blood in the stool in over 40 per cent of cases. Such results were obtained by Kirschen and associates<sup>124</sup> in studying 146 normal persons to whom small divided doses of hemoglobin were administered and whose stools were tested by the routine benzidine slide test. The delicacy of this test is such that unless patients are maintained on strictly meat-free diets, it is doubtful whether a barely positive result is of significance, and great care should be used in the interpretation of such minimal findings. The authors contribute one point of incidental interest, namely, that carmine per se when used for the marking of stools may yield a positive result in a test for blood in the feces. A continuation of previous careful studies on the significance of blood in the stools is reported by Schiff and his collaborators.<sup>125</sup> Observations were made on a group of subjects after the introduction of varying quantities of whole blood into the stomach, and the results of stool examinations were recorded. Tarry stools were obtained in subjects given amounts of blood as small as 200 cc. It was shown that stools may be entirely bloody and never tarry as a result of intestinal hypermotility. Such a confirmation of a clinical fact is reassuring and suggests that a grossly bloody stool does not necessarily indicate hemorrhage from the small intestine or the colon. The number of bloody or tarry stools is not directly related to the amount of blood in the stomach. One patient had five bloody stools after the introduction of 1,000 cc. of blood, whereas another had but three tarry stools after a similar introduction of 2,000 cc. of blood. Bloody stools may be passed for as long as three days and tarry stools for as long as five days after intragastric administration of a single quantity of blood. Positive results of guaiac tests for occult blood in the stools may persist for as long as ten days after the ingestion of 250 cc. of blood. The conclusions, although not new, should be stressed because of their clinical application. From the results of the experiments Schiff and his associates believe that the passage of a tarry stool does not necessarily indicate the occurrence of a severe hemorrhage into the digestive tract and that the persistence of tarry stools or of occult blood in the stools does not necessarily indicate the continuation of such a hemorrhage.

Gross hemorrhage unassociated with pain may be and frequently is encountered in the presence of a peptic ulcer, and as has previously been noted, an elevated individual threshold for pain may explain many of these occurrences. That other causes may be responsible for painless gross bleeding from the stomach or the duodenum is shown in the short

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124. Kirschen, M.; Sorter, H., and Necheles, H.: Occult Blood, with a Note on the Use of Carmine for the Marking of Stools, *Am. J. Digest. Dis.* 9:154, 1942.

125. Schiff, L.; Stevens, R. J., Shapiro, N., and Goodman, S.: Observations on the Oral Administration of Citrated Blood in Man: II. The Effect on the Stools, *Am. J. M. Sc.* 203:409, 1942.



report of Moschcowitz, Mage and Kugel.<sup>126</sup> Of 14 patients who came to necropsy in association with massive gastroduodenal hemorrhage without pain, only 3 had gastrointestinal bleeding from a chronic peptic ulcer. In the other 11 cases there were associated conditions that might be classified as gastritis or as being secondary to more superficial lesions of varied natures. It is quite possible that the superficiality of the lesions in erosions causing even fatal hemorrhage may serve in part as an explanation for the absence of pain.

The therapy of bleeding ulcers is still a matter of choice, if one can judge by the varied results reported in the literature. Nicholson and Miller,<sup>127</sup> in a careful analysis of therapeutic results, express the belief that a prompt feeding program following hematemesis plus administration of a reasonable amount of fluid gives far better results than any other type of treatment. They believe that the type of diet is of secondary importance to the requirement that food be given promptly, irrespective of the degree of bleeding, frequently and in adequate amounts. Their observers also feel strongly that the use of morphine should be strictly avoided because of its effect on the tonicity of the duodenal musculature. They believe that the prompt feeding program is effective probably because it meets nutritional demands; supplies fluid to counteract shock; neutralizes the gastric acidity, thus preventing further erosion in the ulcerated areas, and increases intragastric and intraduodenal pressure, thus tending to close the open and bleeding vessel. Although the mortality figures vary, other authors, such as Eichhorn,<sup>128</sup> Chaikin and Tannenbaum<sup>129</sup> and MacMillan,<sup>130</sup> report similar beneficial results. Eichhorn carried out comparative studies on a series of 81 patients with bleeding ulcers. Thirty-three patients were treated by initial starvation, and the remainder (38) were fed immediately. There were no deaths in the second group of patients, whereas in those treated by initial starvation, there was a mortality of 19 per cent. Eichhorn believes that the principle involved in the Meulengracht regimen greatly lowers the mortality rate, provides more comfort for the patient and results in a shorter stay in the hospital, a statement that is borne out by the results

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126. Moschcowitz, E.; Mage, S., and Kugel, V. H.: Causes of Painless Gastro-Duodenal Hemorrhage, *Am. J. M. Sc.* **202**:48, 1941.

127. Nicholson, J. T. L., and Miller, T. G.: The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer: A Report on Thirty-Two Cases and an Analysis of 1396 Recorded Cases, *Am. J. Digest. Dis.* **8**:446, 1941.

128. Eichhorn, J. P.: Immediate Feeding Versus Initial Starvation in the Treatment of Bleeding Peptic Ulcer, *Am. J. M. Sc.* **203**:428, 1942.

129. Chaikin, N. W., and Tannenbaum, O.: Bleeding Peptic Ulcer: A Clinical Study with Special Reference to the Meulengracht Regimen, *Am. J. Digest. Dis.* **9**:150, 1942.

130. MacMillan, R. L.: Massive Hemorrhage from Stomach: Its Diagnosis and Treatment, *North Carolina M. J.* **2**:476, 1941.

of a more or less similar study by Chaikin and Tannenbaum. Rafsky and Weingarten,<sup>131</sup> on the contrary, state that the mortality rate in a group of patients treated by restricted dietary measures is essentially no different from that in a group treated by the Meulengracht diet. These authors prefer their own method of treatment, which involved starvation for the first day after admission to the hospital, or longer if bleeding continues, following which hourly feedings of cereal or milk were administered, together with the usual supportive measures employed by most physicians. Intraduodenal feeding was employed from the fourth to the seventh day after admission in the presence of pain. Emery,<sup>132</sup> by comparing the results of treating 36 patients with bleeding ulcer by the Meulengracht regimen with the results obtained on a group of 50 patients treated previously by the Sippy regimen, believes that there was no essential difference in the mortality figures. He states that there was no evidence that bleeding stopped any more rapidly on the Meulengracht than on the Sippy regimen, although the former was undoubtedly pleasanter for the patient. In most instances, it can be safely asserted, however, that the principle of early feeding after hemorrhage is to be desired and that in some form or another it constitutes the method of choice, as was indicated some years ago by Andresen. The question of iron therapy in the treatment of the anemia due to gastrointestinal bleeding has always occasioned a certain amount of controversy because of the possible irritative action of iron salts. Ehrenfeld and Wallace<sup>133</sup> believe that colloidal iron hydroxide in combination with aluminum hydroxide may be given continuously without causing any gastric irritation to patients with peptic ulcer and that in those patients with persistent chronic bleeding of a mild character it is possible to maintain a constant red cell count and hemoglobin level by such means.

Schiff and associates<sup>134</sup> continue to stress the prognostic significance of the rise in blood urea nitrogen following hematemesis or melena. Chunn, Harkins and Boals<sup>135</sup> similarly mention the prognostic importance of blood urea determinations in cases of massive bleeding from the upper portion of the gastrointestinal tract. The latter authors, however,

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131. Rafsky, H. A., and Weingarten, M.: Bleeding Peptic Ulcer: Clinical Appraisal of Various Methods of Treatment Based on a Series of Four Hundred and Eight Cases, *J. A. M. A.* **118**:5 (Jan. 3) 1942.

132. Emery, E. S., Jr.: A Comparison of the Meulengracht and Sippy Therapies in the Care of Bleeding Peptic Ulcers, *Am. J. Digest. Dis.* **8**:387, 1941.

133. Ehrenfeld, I., and Wallace, R. P.: Iron as a Therapeutic Supplement in Peptic Ulcer Therapy, *Am. J. Surg.* **53**:470, 1941.

134. Schiff, L.; Stevens, R. J.; Moss, H. K., and Garber, E. S.: The Prognostic Significance of the Blood Urea Nitrogen Following Hematemesis or Melena, *Am. J. Digest. Dis.* **9**:110, 1942.

135. Chunn, C. F.; Harkins, H. N., and Boals, R. T.: Alimentary Azotemia and the Bleeding Peptic Ulcer Syndrome, *Arch. Surg.* **43**:773 (Nov.) 1941.

mention in their article the results of animal experiments in which roentgen nephritis was produced by the method of Hartman. In these animals the administration of blood by stomach tube produced much more prolonged azotemia than that resulting in control animals. Such a finding would seem to confirm the careful observations previously reported by Johnson, who indicated that the degree of azotemia was more dependent on the renal factor than on any others and was of little, if any, prognostic significance. Black<sup>136</sup> stresses the importance of alteration in renal function as a significant factor in the production of azotemia secondary to gastrointestinal hemorrhage, and in addition, presents observations showing that a marked rise in the blood level of amino acid nitrogen occurs at the same time. He suggests that the increase in amino acid nitrogen probably indicates temporary hepatic dysfunction. A general discussion of the biochemical changes associated with hemorrhage from the stomach and the duodenum and a consideration of the necessity of therapeutic measures directed toward an improvement in the urinary excretion of urea is to be found in an article by Bick and Wood.<sup>137</sup>

Possible transient myocardial changes secondary to massive hemorrhage from peptic ulcer are reported by Scherf and his collaborators.<sup>138</sup> Conclusions as to such myocardial damage are based on electrocardiographic changes, which appear within a few hours after the hemorrhage and disappear again after a few days. Obviously, such transient changes are of negligible importance in younger persons, but it is possible that cardiac disturbances may be of prognostic significance in older ones, and clinical experience would seem to indicate that such may occasionally be the case, particularly in the presence of already existing heart disease.

The problem of perforated ulcers is essentially surgical but should be competently faced by the internist, to whom the patient with this condition frequently first presents himself. The survey by Berson<sup>139</sup> is, therefore, of importance. It covers the experiences of an eighteen year period, including 154 consecutive patients with acute ulcer perforations. A relative infrequency was noted during the warm months, and the incidence of perforation in men was thirteen times that encountered in women. More than four fifths of the entire group had experienced ulcer

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136. Black, D. A. K.: Blood Amino Acids in Hematemesis, *Lancet* **2**:309, 1941.

137. Bick, M., and Wood, I. J.: Some Observations on the Biochemical Changes Associated with Hemorrhage from the Stomach and Duodenum, *M. J. Australia* **28**:104, 1941.

138. Scherf, D.; Reinstein, H., and Klotz, S. D.: Electrocardiographic Changes Following Hematemesis in Peptic Ulcer, *Rev. Gastroenterol.* **8**:343, 1941.

139. Berson, H. L.: Acute Perforated Peptic Ulcers: An Eighteen Year Survey, *Am. J. Surg.* **56**:385, 1942.

symptoms prior to surgical intervention, and 3 had had recurrent perforations. Pneumoperitoneum was present in 80 per cent of the cases in which roentgenograms were taken. Perforation of duodenal ulcers was seven times as frequent as that of gastric ulcers, but the mortality was greater in patients with the latter lesions. Seventy per cent of the patients with cultures of peritoneal fluid positive for micro-organisms at the time of operation died. It is highly probable that recently introduced chemotherapeutic agents would have modified these results to an appreciable degree. The total mortality rate was 15 per cent. The importance of the time element in the ultimate result after perforation of an ulcer is illustrated by the report of Henry,<sup>140</sup> who examined the peritoneal fluid obtained from a group of perforated peptic ulcers, micro-organisms being found to be present in the peritoneal cavity shortly after perforation. Gastric acidity is low at the time of operation, and bacteria occur in the gastric contents. The peritoneal fluid has a hydrogen ion concentration and a chloride content approaching those of blood plasma, and there is little evidence that there is any diminution of the bacterial growth either by gastric contents or by peritoneal fluid. Seley and Colp<sup>141</sup> report pathogenic micro-organisms in 30 per cent of benign ulcers studied, but, as usual, one would expect a much higher incidence of bacterial growth occurring in malignant lesions, possibly due to lower gastric acidity.

The role of the surgeon in the ulcer problem is discussed by Wangensteen,<sup>142</sup> who believes that all failures in the management of patients with ulcer treated either by medical or by surgical measures rise from inability to control gastric acidity. Whether such a concept is valid certainly remains an unsettled question at the present time, but his conclusions are undoubtedly correct—that subtotal gastrectomy at present is the most effective surgical procedure in controlling postoperative gastric acidity and is associated with the lowest incidence of postoperative recurrences. He believes that this operation may be done for ulcer and its complications, exclusive of perforation, with an operative risk of 2 per cent, provided adequate preoperative and postoperative measures are taken. A follow-up study by Walters and Cleveland<sup>143</sup> supports the contention that partial gastrectomy offers the best chance

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140. Henry, C. M.: Peritoneal Fluid in Perforated Peptic Ulcers, *Ann. Surg.* **114**:155, 1941.

141. Seley, G., and Colp, R.: The Bacteriology of Peptic Ulcers and Gastric Malignancies: Possible Bearing on Complications Following Gastric Surgery, *Surgery* **10**:369, 1941.

142. Wangensteen, O. H.: The Surgeon and the Ulcer Problem, *Illinois M. J.* **80**:100, 1941.

143. Walters, W., and Cleveland, W. H.: Results of Partial Gastrectomy for Bleeding Duodenal, Gastric and Gastrojejunal Ulcer, *Ann. Surg.* **114**:481, 1941.

of a cure or of an amelioration of symptoms of bleeding peptic ulcer and the best prophylaxis against further hemorrhage. Eighty-seven per cent of 112 patients treated by partial gastrectomy for bleeding peptic ulcer obtained satisfactory results. These authors stress the necessity of removing the pyloric antrum in the course of all gastric resections, in order to obtain the most satisfactory results. Such a view is commonly held by most experienced gastric surgeons, who have tended to become more and more radical in their procedures in recent years. The time that has elapsed since the inauguration of this most radical form of subtotal resection is still too short, in my opinion, to settle this point adequately. An article by Connell,<sup>144</sup> for example, is of interest. He discusses the physiology of the stomach in relation to hydrochloric acid production, with particular reference to Edkin's theory that an antral hormone, gastrin, stimulates the secretion of fundic acid. He states correctly that this theory has not yet been proved either experimentally or clinically, and such doubt is implied in an article previously referred to by Ivy.<sup>31</sup> Connell suggests that subtotal resection be modified by preservation of the alkaline secreting antrum and the pyloric neuromuscular sphincter mechanism. Whether this suggestion is wise may be open to question, but the final conclusion in the light of previous experience in ulcer therapy is undoubtedly correct, namely, that because of various known factors, it is wise to refrain from drawing conclusions relative to results of therapeutic measures until after the lapse of at least five years. To date, follow-up studies of this length are still lacking. There can be no doubt that subtotal resection has reduced remarkably the incidence of recurrent ulcer, and it is true that many patients lead relatively normal comfortable lives after such an operation. It is also true, however, that an important number of persons who have been subjected to such radical surgical procedures recover strength and weight slowly after the operation and for a long time have a multiplicity of minor complaints which should not be overlooked. Subtotal resection is not a physiologic procedure, and it is still wise to question the rationale of such a maneuver in the hope that better surgical measures may be evolved in those cases in which the condition is intractable to medical treatment. Schwartz, Reingold and Necheles,<sup>145</sup> recognizing these facts, have made an investigation of the relation between blood sugar and general complaints following subtotal gastric resection. Their studies were undertaken because of observations on the complaints of dizziness, warmth, perspiration, palpitation and nausea, which are not infrequently residual

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144. Connell, F. G.: Peptic Ulcer, Hydrochloric Acid and Edkins' Theory, *Am. J. Surg.* **53**:255, 1941.

145. Schwartz, A.; Reingold, I., and Necheles, H.: Investigation of the Relationship Between Blood Sugar and General Complaints Following Subtotal Gastric Resection, *Am. J. Digest. Dis.* **9**:151, 1942.

symptoms in patients subjected to subtotal gastrectomy. The studies indicated that they are not due to transient hypoglycemia, but the authors are inclined to attribute them to a distention of the upper portion of the small intestine following the ingestion of food. In many instances they could be prevented by the taking of frequent, small meals or relieved by lying down after the intake of food.

*Gastric Cancer.*—Attempts to produce experimental gastric cancer in animals continue to be made, and a report by Stewart and Lorenz<sup>146</sup> records the production of cancer in mice following local injection of 20-methylcholanthrene. The injections were made into the glandular mucosa of the pyloric portion of the stomach, which is not completely refractory to cancer induction. Unlike the results obtained in the production of tumors in the forestomach and the small bowel, the oral administration of this substance was not accompanied by carcinomatous changes in the pyloric portion of the stomach. Groups of rats and mice studied by Beck and Peacock<sup>147</sup> were fed a variety of repeatedly heated fats in addition to an adequate basal diet. Subsequent avitaminosis A appeared among the animals, and ulceration and papillomatosis of the forestomach were observed among those that died. Control animals did not show any gross pathologic lesions. Whether various factors, such as dietary deficiencies, gastric achlorhydria and the like, lead to the development of papillomatous or malignant changes in human beings is still a completely open question, but the results of experiments, such as the preceding ones, together with numerous clinical observations, would lead one to hope that evidence may eventually be obtained regarding the causative factors.

It is well to review from time to time the results of surgical treatment of malignant disease of the stomach. The results reported by Walters and his colleagues<sup>148</sup> are typical of the relatively successful surgical treatment of malignant growths of the stomach that has been reported in recent years. Examination of the results will show that the mortality rate has been progressively decreasing. In a large group of patients who did not have extensive carcinoma or metastases and who underwent gastric resection, these authors report a five year survival rate of nearly 30 per cent, a ten year survival rate of 20 per cent and a fifteen year survival rate of 15 per cent. An important diagnostic point is found in the statement that approximately one third of the

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146. Stewart, H. L., and Lorenz, E.: Induction of Adenocarcinoma of the Pyloric Stomach in Mice by Methylcholanthrene, *J. Nat. Cancer Inst.* **2**:193, 1941.

147. Beck, S., and Peacock, P. R.: Gastro-Papillomatosis Due to Vitamin A Deficiency Induced by Heated Fats, *Brit. M. J.* **2**:81, 1941.

148. Malignant Lesions of the Stomach, editorial, *J. A. M. A.* **117**:1893 (Nov. 29) 1941.

patients who had carcinomatous lesions of the stomach which were resectable had symptoms of the so-called "ulcer type" and in the majority of these patients routine ulcer therapy resulted in a temporarily effective control of symptoms. Too much emphasis cannot be placed on the latter fact, inasmuch as a favorable result of medical treatment in relatively early cancer too frequently has led to a postponement of adequate diagnostic measures and therapy. The authors urge a more general acceptance of the fact that medical treatment of an ulcer type of dyspepsia should not be instituted without roentgen examination to determine the exact location and nature of the lesion. In a subsequent paper Walters<sup>149</sup> points out the success of subtotal resections in the treatment of benign gastric ulcer, the results being superior to those of similar operations for duodenal ulcer. At the time of publication Walters stated that he had not seen a case of recurrent benign ulceration in which half or more of the stomach was removed with the benign gastric lesion. Eusterman<sup>150</sup> emphasizes the fact that small ulcerating forms of gastric carcinoma not only may be clinically indistinguishable at times from benign lesions but may respond to medical treatment in such a favorable manner as to give an entirely wrong impression of their true nature. Failure to carry out adequate diagnostic procedures under such circumstances cannot be too strongly condemned. Eusterman points out the various diagnostic criteria that eventually lead to a decision as to the form of therapy indicated. It is rather unfortunate that in none of these articles is sufficient prominence given to the diagnostic possibilities of adequate examination by an experienced gastroscopist. Before resorting to radical surgical treatment of gastric ulceration, a combined examination by roentgen and gastroscopic methods undoubtedly offers the best possible control of the situation and in many instances provides perfectly adequate information as to complete healing and as to the benign nature of the lesion, something that frequently cannot be accomplished by roentgen studies alone. Eusterman adds 3 other cases to 2 previously reported of carcinoma *in situ*, a relatively rare condition. A rather discouraging report on the subject is that of Boyce.<sup>151</sup> Over a period of years only 2 of every 30 patients treated for cancer of the stomach in the New Orleans Charity Hospital could be submitted to gastrectomy, and the immediate mortality for this operation was over 50 per cent, the 200 latest surgical patients

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149. Walters, W.: Gastric Ulcer, Carcinomatous Ulcer or Ulcerating Carcinoma? *Ann. Surg.* **115**:521, 1942.

150. Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, *J. A. M. A.* **118**:1 (Jan. 3) 1942.

151. Boyce, F. F.: Carcinoma of the Stomach in a Large General Hospital: A Comparative Study of Two Series of Surgical Cases from Charity Hospital of Louisiana at New Orleans, *J. A. M. A.* **117**:1670 (Nov. 15) 1941.

in this series presenting little improvement in end results over a similar series reported in 1933. The author rightly attributes failure to make early diagnoses for this particular group of patients, most of whom were taken from the lower economic levels, to lack of insistence on the part of physicians on adequate study of gastric complaints. Hinton,<sup>152</sup> in a discussion of the same subject, outlines the difficulties of diagnosis and treatment and also shows the relative rarity with which carcinoma develops in benign ulcer. As an indication of the trend of cancer studies at the present time, he cites the work done by many investigators attempting to find a connection between estrogens, androgens and the gastric mucosa as a possible factor in causation of carcinoma.

As a means of determining the prognosis in gastric carcinoma, the classification based on gastroscopic examination suggested by Baumann is discussed by Schindler and his associates.<sup>153</sup> Inasmuch as careful gastroscopy permits at least a relatively satisfactory use of this classification, it is of interest until further observations and studies have been made. According to this grouping, lesions classified as polypoid or noninfiltrating, carcinomatous ulcers have a relatively good prognosis; those classified as infiltrating, carcinomatous ulcers and diffuse infiltrating growths are associated with unfavorable end results after surgical intervention. That erroneous conclusions may be drawn at operation on the possible spread of gastric cancer to regional lymph nodes is indicated in a careful pathologic study by Coller, Kay and MacIntyre.<sup>154</sup> In 53 cases the lymph nodes were dissected from each operative specimen and examined individually after a rather exhaustive study. Evidence of metastases was found in three fourths of the cases in this study, in one fourth of the cases the growth had involved the duodenum and in one fourth of the cases the upper margin of the neoplasm could not be determined by palpation alone at the time of operation. There was no relation between the size of the neoplasm and the presence of lymphatic metastases. Small neoplasms were often associated with extensive nodal metastases. Fewer metastases were noted from polypoid neoplasms than from those of the sessile type. In a majority of the cases in which the regional nodes were not palpable or if palpable were not thought to be suggestive of a malignant growth, the cancer was subsequently shown to have metastasized. The authors insist on the necessity of including a wide zone of resection, whether palpable lymph nodes are present or not, in order to increase the likelihood of cure.

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152. Hinton, J. W.: Carcinoma of Stomach, Bull. New York Acad. Med. **17**:829, 1941.

153. Schindler, R.; Steiner, P. E.; Smith, W. M., and Dailey, M. E.: The Classification of Gastric Carcinoma, Surg., Gynec. & Obst. **73**:30, 1941.

154. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Stomach, Arch. Surg. **43**:748 (Nov.) 1941.



Justification for the most radical form of surgical treatment, even if it involves total gastrectomy, is to be found in the more recent reports of an increasing number of survivals following operation based on improved surgical technic. Even with complete removal of the stomach, as pointed out by Jones,<sup>155</sup> Donald<sup>156</sup> and Morton,<sup>157</sup> it is possible to hope for a progressively increased survival rate and relative freedom from incapacitating symptoms with adequate postoperative care.

*Duodenum (Sphincter of Oddi).*—The behavior of the sphincter of the common bile duct and its relation to the processes of normal digestion in the intestinal tract have been the subjects of study by Necheles and Kozoll.<sup>158</sup> The resistance of the sphincter and its response to a number of substances were tested on 10 human subjects after operation and drainage of the common bile duct. Parallel experiments were carried out on dogs in which the activity of the gallbladder and the duodenum and sphincter resistance were measured simultaneously. Drugs of the epinephrine group had variable effects on sphincter tone in human subjects and on the mechanism of evacuation of the gallbladder in dogs. Symptoms produced by the administration of atropine were followed by increased sphincter resistance in the patients studied. The effects of papaverine were inconstant. Codeine phosphate also increased sphincter resistance greatly both in the human subjects and in the experimental animals. Prostigmine usually increased sphincter tone considerably. Magnesium sulfate was followed by vigorous contractions both of the sphincter and of the duodenum in the dog but by only a slight increase in sphincter tone in human beings. The hydrochloride of diphenylacetyldiethylaminoethanol, glyceryl trinitrate and amyl nitrite depressed the tone of the sphincter, particularly when it was high after the administration of other drugs like codeine. In the patients studied postoperatively, it was noted that coughing, the occurrence of nausea and passage of stools increased sphincter resistance, as did ingestion of a meal. The sphincter seemed to be subject to psychologic effects, inasmuch as the sight or odor of meals produced considerable tonus waves. These results are probably to be accepted as an accurate interpretation of physiologic responses occurring in normal human beings, but it should be remembered that in half of the experiments made on

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155. Jones, T. E.: Total Gastrectomy: Report of a Case, *Cleveland Clin. Quart.* **8**:225, 1941.

156. Donald, C. J., Jr.: Total Gastrectomy: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **16**:446, 1941.

157. Morton, C. B., II: Total Gastrectomy: Indications for Operation with a Report of Four Cases, *Arch. Surg.* **44**:72 (Jan.) 1942.

158. Necheles, H., and Kozoll, D. D.: A Study of the Sphincter of Oddi in the Human and in the Dog, *Am. J. Digest. Dis.* **9**:36, 1942.

patients in this particular study surgical treatment of the gallbladder had already preceded observation and may have modified the responses to some extent.

The effect of bile flow through the sphincter, probably as a result of relaxation of the sphincter, was observed by Bergh<sup>159</sup> in human subjects, with results confirming the suggestions of previous investigators. A fatty meal, consisting of egg yolks and cream, apparently produced relaxation of the sphincter, but fresh olive oil had little effect. After a protein meal relaxation occurred only once, and no significant effect was observed after ingestion of carbohydrates.

Focal disease limited to the sphincter of the common bile duct is rare. For this reason the report of Sharpe and Comfort<sup>160</sup> on 40 cases of carcinoma of the papilla of Vater is worthy of study. In only 1 of these cases was the possibility of carcinoma of the ampulla suggested before operation, although in 38 the diagnosis indicated that the clinician knew that obstruction of the common bile duct was present. Obviously, jaundice was a constant feature, but in many instances it was protracted and was fluctuating in its intensity. The authors point out that there is no typical clinical picture or no typical physical findings. Pain is a constant feature, and it is of extreme interest that chills and fever were present in over half of the cases, as was diarrhea. The obvious conclusion from such a study is that in the absence of clinical improvement or adequate diagnostic observations surgical intervention is indicated.

*Diverticula and Unusual Tumors.*—It is usually admitted that diverticulosis of various portions of the digestive tract may represent an adventitious condition and may not cause any symptoms. This is particularly true of diverticula of the stomach and the upper portion of the small intestine. Gastric diverticula are rare, and as a rule, they are encountered near the cardiac orifice, as is pointed out by Reineke,<sup>161</sup> who reports 4 cases of gastric diverticulum so situated. The diagnosis is dependent on roentgen examination, and treatment when necessary may involve simple medical measures, including postural drainage or, occasionally, resection. Two other instances of this uncommon condition are reported by Schmidt and Walters,<sup>162</sup> who review the classification and symptomatology in detail. They believe that gastroscopy is

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159. Bergh, G. S.: The Effect of Food Upon the Sphincter of Oddi in Human Subjects, *Am. J. Digest. Dis.* **9**:40, 1942.

160. Sharpe, W. S., and Comfort, M. W.: Carcinoma of the Papilla of Vater: Clinical Features in Forty Cases, *Am. J. M. Sc.* **202**:238, 1941.

161. Reineke, H. G.: Diverticula of the Upper End of the Stomach, *Am. J. Roentgenol.* **46**:650, 1941.

162. Schmidt, H. W., and Walters, W.: Diverticula of the Stomach, *Am. J. Surg.* **52**:315, 1941.

of aid in differentiating the types of diverticula and in demonstrating the presence or absence of pancreatic tissue or benign growths in those instances in which the diverticula are essentially of the traction type. Kozinn and Jennings<sup>163</sup> add a case to the small number of previously reported instances of jejunal diverticula. Like other diverticula they are usually thought to be either congenital or acquired. The authors correctly point out the lack of symptoms attributable to most of these abnormalities, but, as in the case they report, they may cause either acute abdominal conditions due to perforation and peritonitis or bleeding, the latter being more common in children.

Meckel's diverticulum is a relatively common condition and frequently results in bleeding in children or in obstructive symptoms. Two instances of such an occurrence are reported by Conrad.<sup>164</sup> A different type of complication is mentioned by Maddock and Coventry<sup>165</sup> in a case report of perforation of an ulcer of the ileum occurring opposite a Meckel diverticulum in a young child, another rather characteristic complication of this condition. As is frequently true, in this case and in 2 reported by Waugh and his colleagues<sup>166</sup> heterotopic gastric mucosa was present in the diverticulum, with resulting peptic ulceration of the ileum opposite the stoma. An unusual complication is that reported by Lium and Ladd<sup>167</sup> in an elderly man in whom acute Meckel's diverticulitis complicated a strangulated left inguinal hernia. Occasionally, Meckel diverticula are complicated by the local appearance of new growths. Albright and Sprague<sup>168</sup> add another to 6 previously reported cases of primary adenocarcinoma arising in such a diverticulum. Koucky and Beck<sup>169</sup> report a still more rare condition, a perforated leiomyoma of a Meckel diverticulum.

Unusual forms of growth, benign or otherwise, occur with sufficient frequency at various levels in the gastrointestinal tract to warrant only passing comment. Because of the variety of conditions involved, how-

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163. Kozinn, P. J., and Jennings, K. G.: Jejunal Diverticulitis: Its Occurrence in a Two-Year-Old Girl, *Am. J. Dis. Child.* **62**:620 (Sept.) 1941.

164. Conrad, N. A.: Meckel's Diverticulum: Report of Two Cases, *Am. J. Surg.* **52**:267, 1941.

165. Maddock, W. G., and Coventry, M. B.: A Perforated Ulcer of the Ileum Opposite a Meckel's Diverticulum, *Surg., Gynec. & Obst.* **73**:105, 1941.

166. Waugh, J. M.; Herrell, W. E., and Crumpacker, L. K.: Peptic Ulcer in Meckel's Diverticulum Causing Intrinsic Intestinal Obstruction: Report of Two Cases, *Surgery* **11**:385, 1942.

167. Lium, R., and Ladd, S. T.: Left Inguinal Hernia with Acute Meckel's Diverticulitis and Peritonitis, *New England J. Med.* **226**:15, 1942.

168. Albright, H. L., and Sprague, J. S.: Primary Adenocarcinoma in a Meckel's Diverticulum, *New England J. Med.* **226**:142, 1942.

169. Koucky, J. D., and Beck, W. C.: Perforated Leiomyoma of Meckel's Diverticulum: Report of Case, *Surgery* **10**:636, 1941.

ever, it is worth while to enumerate some of them briefly, particularly because the diagnosis of tumor of the digestive tract is being made with a rapidly increasing frequency. Rumold<sup>170</sup> contributes examples of an extremely rare condition, submucous lipoma of the stomach, 32 cases having been recorded in the literature prior to his report. Lemon and Broders<sup>171</sup> give a fairly comprehensive clinical and pathologic study of leiomyosarcoma, hemangioendothelioma, or angiosarcoma, and fibrosarcoma of the stomach. Fourteen cases of histologically proved gastric sarcoma are included in the report. Surgical removal of these tumors is, of course, indicated, and the prognosis, while guarded, is better than that of lymphosarcoma or carcinoma. A leiomyoma of the stomach was successfully removed by Halperin,<sup>172</sup> and reports of 2 successful operations on gastric hemangiomas are added by Morton and Burger,<sup>173</sup> in 1 case the growth being found on gastroscopy. A report by Koenig and Culver<sup>174</sup> of 2 cases of Hodgkin's disease involving the stomach confines itself largely to a description of the roentgen findings, which unfortunately are not sufficiently characteristic to differentiate this condition from other infiltrating ulcerative lesions. Another rare occurrence is acute perforation of lymphosarcomatous ulcer of the stomach, mentioned by Koucky and his associates.<sup>175</sup> Symptoms in a boy of 14 years were of only one week's duration before the acute perforation took place. The nature of the ulcerative process was determined at operation by biopsy, and satisfactory recovery occurred. In spite of the repeated statement that perforation is a common complication of gastric lymphosarcoma, so far the authors have found only 4 other instances of a similar occurrence. One of the rarest forms of gastric tumor is recorded by Fuller,<sup>176</sup> who describes a case of neurilemmoma of the wall of the stomach complicated by ulceration of the underlying mucosa. The clinical picture in this instance was that of peptic ulcer. The report is of further interest in that it brings out a point that is occasionally forgotten—namely, that new growths, either primary or benign, may

170. Rumold, M. J.: Submucous Lipomas of the Stomach, *Surgery* **10**:242, 1941.

171. Lemon, R. G., and Broders, A. C.: A Clinical and Pathological Study of Leiomyosarcoma, Hemangioendothelioma or Angiosarcoma, and Fibrosarcoma of the Stomach, *Surg., Gynec. & Obst.* **74**:671, 1942.

172. Halperin, P. H.: Leiomyoma of the Stomach, *Missouri M. J.* **38**:235, 1941.

173. Morton, C. B., and Burger, R. E.: Hemangioma of the Stomach: Review of the Literature and Report of Two Cases, *Surgery* **10**:891, 1941.

174. Koenig, E. C., and Culver, G. J.: Hodgkin's Disease Involving the Stomach: Report of Two Cases, *Am. J. Roentgenol.* **46**:827, 1941.

175. Koucky, J. D.; Beck, W. C., and Atlas, J.: Acute Perforation of Lymphosarcomatous Ulcer of the Stomach, *Ann. Surg.* **114**:1112, 1941.

176. Fuller, R. H.: Neurilemmoma of the Stomach with Peptic Ulcer, *Arch. Path.* **32**:441 (Sept.) 1941.

cause superficial ulceration of the gastric mucosa, with a resulting clinical picture entirely similar to that of peptic ulcer. Unless careful diagnostic procedures are carried out, the underlying cause of the disease is frequently overlooked because of the favorable response to medical therapy. In this case the tumor and the ulcer were resected, with subsequent recovery. Another curious occurrence is noted by Cohn and associates,<sup>177</sup> who encountered gastric disease in a patient who had been ingesting a preparation containing kaolin for a long time. Clinical and roentgen examination failed to reveal any gastric abnormality, but gastroscopy indicated a prepyloric tumor, which, however, was not seen in the gross resected stomach. Microscopic studies proved the lesion to be a granuloma, with the type of foreign body giant cell present in the lesions of silicosis. Mineralogic studies confirmed the presence of silica in the gastric tissues. The authors were able to reproduce in rabbits similar lesions secondary to silica irritation.

The relative rarity of tumors of the small intestine is indicated in a statistical study of such lesions by Morison,<sup>178</sup> who reviews the results of 2,434 autopsies and 10,705 biopsies. In this large number of specimens examined 21 primary tumors of the small bowel were encountered among which were 5 lipomas, 3 adenomas, 2 leiomyomas, 1 pedunculated subserous fibroma, 2 argentaffinomas, 4 adenosarcomas and 4 lymphosarcomas. In addition, there were 4 examples of pancreatic heterotopia. There is nothing new in the article, but it illustrates more or less clearly the incidence and occurrence of various forms of unusual tumor in the small bowel, a preoperative diagnosis of the nature of which is rarely possible. Obstructive symptoms ranging from mild peristaltic unrest to acute intussusception are frequently encountered, however, and hemorrhage is not uncommon. A similar report is that by Morrison and Donath,<sup>179</sup> who record 45 tumors of the small bowel that were encountered in the examination of over 25,000 autopsy reports and a large number of reports of surgical procedures and biopsies. There were 26 malignant and 19 benign tumors; they were of varying types, as was the case in Morison's report. The incidence of submucous lipoma of the small intestine is apparently greater than that noted in the stomach, and Botsford and Newton<sup>180</sup> report a case of intussusception due to this condition and review 95 other cases of a similar condition.

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177. Cohn, A. L.; White, A. S., and Weyrauch, H. B.: Kaolin Granuloma of the Stomach, *J. A. M. A.* **117**:2225 (Dec. 27) 1941

178. Morison, J. E.: Tumors of the Small Intestine, *Brit. J. Surg.* **29**:139, 1941.

179. Morrison, W. A., and Donath, D.: Tumors of the Small Intestine, *California & West. Med.* **55**:235, 1941.

180. Botsford, T. W., and Newton, F. C.: Intussusception in an Adult Due to Submucous Lipoma of the Ileum, *Surgery* **10**:265, 1941.

Golden and Stout<sup>181</sup> present a careful discussion of one rare type of tumor of the gastrointestinal tract—namely, that originating in the smooth muscle of the tract itself or in the retroperitoneal tissue. Sixty cases of it are described, in 30 of which the tumor was accidentally encountered at operation or at autopsy. The paper concerns itself chiefly with 30 cases in which presenting symptoms were due to the tumor. The distribution in this series was as follows: stomach, 8; duodenum, 2; jejunum, 1; ileum, 3; a Meckel diverticulum, 1; colon, 2; rectum, 5, and retroperitoneal space, 8; two thirds of the tumors were malignant. In discussing the prognosis following adequate surgical treatment the authors make the important point that the outlook depends as much on the anatomic site of the tumor as on its histologic character. Tumors of the stomach, jejunum, ileum and colon are restrained for a long time by the barrier of the peritoneum, so that they can be entirely removed, usually with success. The anatomic peculiarities of the duodenum, rectum and retroperitoneum render difficult or impossible complete removal. Warren and Lulenski<sup>182</sup> present the results of a study of 28 cases of primary solitary lymphoid tumors encountered in a series of 3,132 malignant lesions of the digestive tract. Half of these occurred in the stomach. In this series the prognosis of this solitary form was little better than that of generalized lymphoid tumors, but in their discussion the authors point out that in many cases long survival periods and possibly complete cures have been obtained by adequate surgical treatment and radium therapy.

Only 3 proved cases of primary cancer of the duodenum were encountered among 16,000 admissions to a hospital for patients with cancer, according to Ritvo and Hewes.<sup>183</sup> The symptoms and the roentgen evidence associated with this almost entirely hopeless condition are described by the authors. An odd case of Hodgkin's disease involving the duodenum is reported by Pusch.<sup>184</sup> Successful removal of primary adenocarcinoma of the jejunum is reported by Cornell and Hauser<sup>185</sup> and by Craig,<sup>186</sup> and a general discussion of this particular condition is included in the reports. Sarcoma of the small bowel is

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181. Golden, T., and Stout, A. P.: Smooth Muscle Tumors of the Gastro-intestinal Tract and Retroperitoneal Tissues, *Surg., Gynec. & Obst.* **73**:784, 1941.

182. Warren, S., and Lulenski, C. R.: Primary, Solitary Lymphoid Tumors of the Gastro-Intestinal Tract, *Ann. Surg.* **115**:1, 1942.

183. Ritvo, M., and Hewes, F. L.: Clinical and Roentgen Manifestations of Carcinoma of the Duodenum, *Radiology* **38**:7, 1942.

184. Pusch, L. C.: Hodgkin's Disease of the Duodenum, *Pennsylvania M. J.* **45**:20, 1941.

185. Cornell, N. W., and Hauser, L. A.: Primary Adenocarcinoma of the Jejunum, *Am. J. Surg.* **53**:177, 1941.

186. Craig, W. J.: Primary Carcinoma of the Jejunum: A Case Report, *Brit. J. Radiol.* **14**:162, 1941.

thoroughly discussed by Frank, Miller and Bell,<sup>187</sup> who add 4 cases to the 114 previously reported. An illustration of the difficulty underlying the diagnosis of tumor of the small bowel is presented by Shulman.<sup>188</sup> This author reports a case of primary lymphosarcoma of the jejunum in which approximately 4 feet (122 cm.) of the intestine was involved, without producing anything but mild symptoms. The discovery of the growth was based on a routine roentgen examination for a suspected peptic ulcer.

A complete discussion of the various aspects of carcinoids of the appendix is found in a report by Wengen.<sup>189</sup> He reviews his own 14 cases observed in the Basel Clinic, Basel, Switzerland, and comments on the variety of terms that have been used to designate these essentially benign tumors, which in most instances are completely cured by appendectomy. Gault and Kaplan<sup>190</sup> add another case to 129 previously reported instances of submucous lipomas of the colon. These tumors have the characteristic complication of intussusception in a fairly high percentage of cases, and the authors comment correctly on the fact that in cases of suspected pathologic conditions in the colon in which there is a long history of recurring attacks of pain, constipation and bloody diarrhea, unassociated with loss of weight or with cachexia, the presence of a benign lesion should be suspected. Hemangioma of the large bowel has been reported in only 20 instances, according to Hunt,<sup>191</sup> who included 2 of his own cases in this number, 1 involving the cecum and appendix and encountered in the course of routine cholecystography for gallstones and the other occupying the rectosigmoid portion of the colon and the entire rectum. The predominant symptom obviously is hemorrhage, and the author points out that unlike hemangioma of the small bowel, intussusception has not been reported in association with colonic lesions.

An additional cause of hematemesis and melena is included in this section, namely, hereditary hemorrhagic telangiectasis. Griggs and Baker<sup>192</sup> report 3 cases of this unusual familial condition. The bleeding, as usual, was believed to be due to telangiectatic areas in the stomach or elsewhere in the intestinal tract.

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187. Frank, L. W.; Miller, A. J., and Bell, J. C.: Sarcoma of the Small Intestine, *Ann. Surg.* **115**:544, 1942.

188. Shulman, S.: Primary Lymphosarcoma of the Jejunum, *Am. J. Roentgenol.* **46**:182, 1941.

189. Wengen, H. C.: Aspects of Carcinoids of Appendix, *Klin. Wchnschr.* **20**: 316, 1941.

190. Gault, J. T., and Kaplan, P.: Submucous Lipoma of the Colon: Report of Case, *Am. J. Surg.* **53**:145, 1941.

191. Hunt, V. C.: Hemangioma of the Large Bowel, *Surgery* **10**:651, 1941.

192. Griggs, D. E., and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding, *Am. J. Digest. Dis.* **8**:344, 1941.

*Intestinal Obstruction.*—The problem of intestinal obstruction has received considerable attention, both from the point of view of experimental investigation and from that of clinical observation. Antoncic and Lawson<sup>193</sup> carried out balloon studies of motility in obstructed loops of small bowel in unanesthetized dogs. Comparisons were made in some of the animals with the motility in unobstructed distal segments. The range of pressure in closed loops was found to be considerably above the range in the distal, unobstructed intestine. Contractility was usually considerably greater in the obstructed loops, and neither pressure nor contractility was found to diminish toward the end of the survival period unless perforation occurred. There was no loss in irritability to intravenous administration of epinephrine, even in the terminal stages of obstruction. These results are in agreement with those of previous investigators, and the data suggest that terminal ileus is a concomitant of peritonitis, rather than of obstruction. The authors were unable to obtain evidence supporting Alvarez' hypothesis that reversal of the rhythmic gradient is responsible for stasis and vomiting in cases of intestinal obstruction.

The mechanism of deflation hyperemia in the intestine was carefully studied by Lawson,<sup>194</sup> who found that the increased arterial flow into loops of small intestine following periods of low pressure distention (deflation hyperemia) is associated with an augmented venous flow and usually is considerably greater in volume than the demonstrable reduction in volume of the intestinal walls during the distention. He considers that the greater part of the deflation hyperemia is due to a persistence of a resistance-lowering mechanism set up by stretch of the intestinal walls. Gatch and Battersby<sup>195</sup> also studied the effect of bowel injury by distention with particular relation to its effect on the volume and concentration of the blood. Distention great enough to injure the bowel is described as passing through two stages noted in human beings and in experimental animals. In the first stage the bowel is tense and anemic; in the second stage it is flaccid and congested. It passes from the first to the second stage when the wall stretches enough to permit resumption of the flow of the blood in fair volume through its capillaries. Injury occurs in the first stage; recovery, in the second. Most of the albuminous fluid encountered in the peritoneal cavity in the presence of obstruction of the bowel accumulates in the first stage of distention and varies with the duration of this first stage and with the degree of

193. Antoncic, R. F., and Lawson, H.: The Muscular Activity of the Small Intestine, in the Dog, During Acute Obstruction, *Ann. Surg.* **114**:415, 1941.

194. Lawson, H.: The Mechanism of Deflation Hyperemia in the Intestine, *Am. J. Physiol.* **134**:147, 1941.

195. Gatch, W. D., and Battersby, J. S.: The Two Stages of Bowel Distention: Study of Bowel Injury by Distention and Its Effect on the Volume and Concentration of the Blood, *Arch. Surg.* **44**:108 (July) 1942.



obstruction to the flow of blood in the wall of the distended bowel. The protein content of peritoneal fluid is about half that of plasma, and it is suggested that damage to the capillaries by intestinal distention is evidently not so serious as that due to burns or to inflammation, which makes the capillary endothelium incapable of holding back the large globulin molecules. The cyanosis of the bowel in the second stage of distention is due to vasomotor paralysis and to the relaxation of the tissues which support the capillaries. The authors believe that it is not due to venous obstruction.

Lawson and Ambrose<sup>196</sup> also studied the utilization of blood oxygen by the distended intestine and showed that during moderate distention of the ileum and the jejunum in dogs, there is usually a marked rise in the oxygen content of the venous blood returning from the loop, with a striking reduction in the arteriovenous oxygen difference. The authors offer their data as incomplete evidence for the opening of low resistance vascular shunts in the distended intestine, which short circuit some of the tissues of the intestinal wall, depriving them of their oxygen supply, and which at the same time provide for the maintenance of an undiminished total volume flow of blood. Gatch and Battersby<sup>197</sup> also report the results of studies on the effect of asphyxia caused by distention of the bowel on the concentration of the blood. Prolonged distention of the stomach and the small bowel, with pressures too low to damage these organs, was found to result in the death of the experimental animals. These investigators believe that asphyxia due to interference with respiration was the cause of death and state that all of the effects of distention can be produced by prolonged limitation of air supply. Blood concentration, which was observed in these experiments, did not seem to be the primary cause of death and could be prevented by the administration of adequate quantities of plasma. Distention of the stomach was more rapidly fatal than distention of the small bowel, whereas distention of the large bowel was comparatively harmless. The lethal effects of such maneuvers seemed to depend on the degree of interference with respiration caused by local areas of distention.

Schnedorf and Orr<sup>198</sup> studied the effect of distention of the small intestine on the flow of bile and of urine in dogs. As has already been

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196. Lawson, H., and Ambrose, A. M.: The Utilization of Blood Oxygen by the Distended Intestine, *Am. J. Physiol.* **135**:650, 1942.

197. Gatch, W. D., and Battersby, J. S.: Effect of Asphyxia Caused by Bowel Distention on the Concentration of the Blood, *Arch. Surg.* **44**:319 (Feb.) 1942.

198. Schnedorf, J. G., and Orr, T. G.: The Effect of Small Intestinal Distention upon Bile and Urine Flow: Its Possible Relationship to the Hepatorenal Syndrome, *Am. J. Digest. Dis.* **8**:303, 1941; The Effect of Distention of the Small Intestine, Anoxemia and Oxygen Therapy upon the Flow of Bile and Urine in the Dog: Relationship to the Hepatorenal Syndrome, *Surg., Gynec. & Obst.* **74**:446, 1942.

noted in distention of the large bowel, hepatic function was seen to be impaired, as evidenced by reduction in the flow of bile. In these experiments a somewhat similar reduction of renal function was also observed, apparently as a later phenomenon. Reductions in bile flow of as great as 40 per cent below the control level were obtained as a result of increased intraenteric pressures, and a further decrease was noted when intestinal distention was produced sufficient to cause a real decrease in the flow of portal blood. Oxygen therapy lessened this inhibition in bile flow in all of the dogs treated. The authors feel that inhibitory nervous reflex, decreased blood flow and anoxemia probably are factors involved in decreasing hepatic function in conditions of intestinal obstruction. Inhalations of high concentrations of oxygen are thought to be indicated when anorexia, with a resulting tendency to acholia and anuria, is observed in cases of intestinal obstruction. Whether or not such a mechanism is operative in the so-called "hepatorenal syndrome," as suggested by Shnedorf and Orr, is highly speculative.

The phenomenon of so-called "leukocyte exhaustion" in intestinal obstruction is discussed by Harris and Feldheym<sup>199</sup> and by Van Duyn.<sup>200</sup> The former authors report a series of 10 cases of obstruction of the small bowel in which daily postoperative white cell counts showed marked leukopenia in the immediate postoperative period of one to seven days. This leukopenia was not associated with surgical sepsis and did not necessarily indicate a fatal prognosis. Van Duyn contributes more detailed comments on the role of abdominal distention in leukocyte exhaustion and cites the results of white cell studies in 6 cases of leukocytic exhaustion with abdominal distention in the absence of severe infection. The so-called "pure degenerative" blood picture, that is, one associated with leukopenia not combined with severe infection, is characterized by low to leukopenic white cell counts, normal to neutropenic percentages of neutrophils, absence of myelocytes, normal to increased percentages of lymphocytes and monocytes and presence of eosinophils. Schilling has previously pointed out that such a differential count does not constitute an unfavorable clinical finding. Such a "degenerative" type of white cell failure may also be encountered in diseases of the gastrointestinal tract, other than those associated with obvious abdominal distention, such as typhoid, dysentery and colitis. On the other hand, Van Duyn believes that a shift to the so-called mixed "degenerative-regenerative" picture, in which regenerative elements or conditions are encountered, such as neutrophilia, myelocytes, monocytopenia and the absence of eosinophils, is usually of serious prognostic significance.

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199. Harris, F. I., and Feldheym, J. S.: Leukocyte Exhaustion in Intestinal Obstruction, *Am. J. Surg.* **54**:417, 1941.

200. Van Duyn, J., II: Role of Abdominal Distention in Leukocyte Exhaustion, *Arch. Surg.* **44**:339 (Feb.) 1942.

Auscultation of the abdomen has been employed for many years in an attempt to obtain further information as to the presence or absence of an obstructive process or of peritonitis with paralytic ileus. Stevens<sup>201</sup> discusses this method of examination and attempts to prove that it may be a valuable adjunct to other diagnostic methods in cases of early intestinal obstruction and acute appendicitis. The author believes that as long as peristaltic sounds are heard, the bowel is not completely devitalized and, therefore, a good chance for recovery exists. In the case of intestinal obstruction, variations in the quality and the activity of peristaltic sounds are discussed in relation to morbid changes in the bowel. Whether such nice conclusions can be drawn in individual cases is open to some doubt, but there is little doubt that abdominal auscultation is used too infrequently both by surgeons and by internists in an attempt to clarify the status of any given cause of abdominal distention. The article is of importance merely to renew interest in an approved but not sufficiently utilized diagnostic method. An excellent and complete review of the clinical aspects of intestinal obstruction and strangulation is presented by Aird.<sup>202</sup> The article should be of interest primarily to the surgeon, but because of its completeness it should be read by the general physician as a help in evaluating the morbid influences underlying intestinal obstruction and strangulation. One possible aid in the diagnosis of strangulation of the bowel is considered by Hill and his collaborators.<sup>203</sup> As has occasionally been noted clinically, peritoneal aspiration in the presence of a strangulated bowel not infrequently yields a profuse exudate, which is cherry red or pink. Hill and his associates produced strangulated loops of bowel in dogs and within four hours were able to demonstrate the presence of a peritoneal exudate of this character. The exudate was extremely toxic when injected intravenously into another animal and always contained micro-organisms. Such a diagnostic procedure, although not usually necessary, should not be overlooked in an occasional case in which the diagnosis is difficult.

Various types of gastrointestinal obstruction, partial or complete in degree, with clinical comments are scattered throughout the literature. One unusual occurrence is that noted by O'Donnell and Klein,<sup>204</sup> who report a case of congenital pyloric stenosis occurring in both members

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201. Stevens, N. C.: The Value of Auscultation of the Abdomen in Intestinal Obstruction, *New England J. Med.* **226**:87, 1942.

202. Aird, I.: Morbid Influences in Intestinal Obstruction and Strangulation, *Ann. Surg.* **114**:385, 1941.

203. Hill, F. C.; O'Loughlin, B. J., and Stoner, M.: Peritoneal Aspiration in the Diagnosis of Strangulated Bowel, *Surg., Gynec. & Obst.* **74**:121, 1942.

204. O'Donnell, F. T., and Klein, J. M.: Pyloric Stenosis in Nonidentical Twins, *Am. J. Dis. Child.* **62**:1025 (Nov.) 1941.

of a set of nonidentical twins. They also mention 2 brothers with this condition, who were operated on two years apart. A table of cases of similar conditions previously reported in the literature is appended. The authors infer that these cases afford additional evidence in support of the theory of the hereditary pathogenesis of some tumors. Congenital duodenal obstruction is an uncommon condition, which is highly fatal in the absence of prompt diagnosis and treatment. White and Collins<sup>205</sup> give the details of 4 cases in which they personally treated the patients and point out the important diagnostic and therapeutic considerations. The presence of bile in the vomitus, which is a persistent symptom, should lead to a suspicion of obstruction below the common bile duct, and the advisability of a careful but relatively simple roentgen examination is properly considered. Operative procedures, which afford the only proper therapeutic measure, should be accompanied by careful treatment of dehydration and shock, plasma transfusions being particularly indicated.

The whole question of intestinal obstruction from gallstones is again discussed by Foss and Summers,<sup>206</sup> who summarize the essential clinical features of such a condition. Of a collective series of 150 patients suffering from such a complication, 15 per cent did not present a history suggestive of disease of the gallbladder. The usual site of obstruction is in the terminal portion of the ileum, the gallstones having almost always passed through a spontaneous cholecystoduodenal fistula. A most unusual manifestation of this condition is mentioned by Cahill,<sup>207</sup> who reports a case of obstruction of the sigmoid flexure of the colon by a large biliary calculus.

Paralytic ileus is not usually associated as a complication accompanying trauma with resulting fractured ribs. Altemeier and Wadsworth<sup>208</sup> discuss 10 cases of such a condition occurring among 454 patients with fractured ribs in whom paralytic ileus was a serious complication. Only 5 cases have been previously reported. In 8 of the 10 cases of ileus following rib fracture the break occurred within 5 cm. of the lateral vertebral border, and the authors speculate on the probability of the intestinal obstruction being associated with an irritation of the thoracic sympathetic ganglions and the splanchnic nerves. Experimental stimulation of the splanchnic nerves produced relaxation and cessation of move-

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205. White, C. S., and Collins, J. L.: Congenital Duodenal Obstruction, *Arch. Surg.* **43**:858 (Nov.) 1941.

206. Foss, H. L., and Summers, J. D.: Intestinal Obstruction from Gallstones, *Ann. Surg.* **115**:721, 1942.

207. Cahill, J. A.: Obstruction of the Sigmoid Flexure by a Large Stone, *Am. J. Surg.* **52**:285, 1941.

208. Altemeier, W. A., and Wadsworth, G. H.: Ileus Following Fractured Ribs, *Ann. Surg.* **115**:32, 1942.

ment of the small bowel. The authors suggest that if the presence of a ruptured intra-abdominal viscus can be ruled out, such a complication of trauma is best treated without operation.

Mattson and Larson<sup>209</sup> comment on a frequently unsuspected cause of intestinal obstruction, namely, food itself. They point out that many cases of so-called "ptomaine poisoning" and intestinal upsets due to food in reality may be short-lived intestinal obstruction due to a food bolus. As proof of such a hypothesis 2 cases of intestinal obstruction due to a large bolus of food, proved at operation, are recorded. Colp<sup>210</sup> discusses 5 cases of obstruction of the large intestine, in which a preoperative diagnosis of a malignant growth was made but in which subsequent developments warranted the diagnosis of muscular spasm as the cause of obstruction. Acceptance of such a mechanism as the cause of lasting intestinal obstruction may seem somewhat unwarranted unless adequate diagnostic procedures are carried out. It would seem that in most instances such a diagnosis would rarely be tenable, but the author's description of individual cases is reasonably convincing, and the article is highly provocative. When one considers the intense and lasting spasm caused by compounds containing lead or morphine and the sharply localized areas of intense spasm that can be easily palpated in patients suffering from acute attacks of "mucous colitis," it does not appear altogether improbable that an occasional case of colonic obstruction may occur from spasm alone.

A clinical diagnosis of acute cecal volvulus is seldom made, since there are no diagnostic criteria that are pathognomonic of this condition. Such a possibility must be considered in cases of intestinal obstruction of obscure origin, however, and for this reason the reports of Browne and McHardy<sup>211</sup> and of Wolfer and his associates<sup>212</sup> should be mentioned. The mechanism underlying such an occurrence is not difficult to visualize when one considers the large number of mobile cecums observed in routine roentgen examinations.

An unusual type of intussusception is that reported by Rossien,<sup>213</sup> who cites a case of chronic, spontaneous, reducing and relapsing

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209. Mattson, H., and Larson, E. A.: Intestinal Obstruction Due to Food, *Minnesota Med.* **24**:559, 1941.

210. Colp, R.: Colonic Spasm as Cause of Intestinal Obstruction, *Surgery* **10**:270, 1941.

211. Browne, D. C., and McHardy, G.: Acute and Chronic Cecal Volvulus, *Am. J. Digest. Dis.* **9**:177, 1942.

212. Wolfer, J. A.; Beaton, L. E., and Anson, B. J.: Volvulus of the Cecum. Anatomical Factors in Its Etiology: Report of a Case, *Surg., Gynec. & Obst.* **74**:882, 1942.

213. Rossien, A. X.: Intussusception: Report of an Unusual Adult Case. *Am. J. Roentgenol.* **46**:832, 1941.

intussusception of the transverse colon into the hepatic flexure. The condition was observed by roentgen examination and correctly interpreted. A simple surgical maneuver of possible value is mentioned by Ireland,<sup>214</sup> who refers to injections of glycerin given to 2 patients with irreducible intussusceptions. In each instance the substance was injected between the intussusciens and the intussusception, with successful subsequent reduction.

There can be little doubt that intestinal suction has proved of inestimable therapeutic value in the treatment of an important number of cases of intestinal obstruction since the method was introduced by Wangensteen. The addition of the Miller-Abbott tube has rendered still further help in the treatment of selected cases of this disorder. There is still at times confusion as regards the proper indications for intestinal intubation and constant suction. An excellent résumé is presented by Abbott<sup>215</sup> and should be read by all practicing physicians. In this article the diagnostic and therapeutic indications for intubation are clearly given. An indication of the value of intestinal suction in the treatment of intestinal obstruction is provided in an article by Blodgett.<sup>216</sup> This author contrasts the mortality occurring in 206 cases of mechanical obstruction in which treatment was without intestinal suction with the results obtained in 151 cases of a similar condition treated by intubation. For the former group the mortality was 17.3 per cent, whereas in the cases in which treatment was by intubation a lowering of the death rate to 7.9 per cent was obtained. Similarly, the mortality in 56 cases of obstruction with associated peritonitis in which treatment was without intestinal suction was 73 per cent, whereas in an almost equal group of cases in which treatment was with the aid of intubation the mortality was only 25 per cent. It is unfortunate that neither of these writers points out the dangers attending too enthusiastic intubation and suction of intestinal contents in cases of obstruction. There can be little doubt that such a measure is of great value therapeutically, but there can also be no question that in many instances too prolonged and too enthusiastic withdrawal of intestinal fluids above an obstructed area may lead to serious, if not fatal, results because of depletion and the postponement of adequate surgical treatment. In addition to the loss of electrolytes accompanying too enthusiastic and prolonged intestinal suction, there is the danger of hypoprothrombinemia, with resultant risk of spontaneous hemorrhage.

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214. Ireland, J.: Treatment of Intussusception, *Arch. Surg.* **43**:418 (Sept.) 1941.

215. Abbott, W. O.: Indications for the Use of the Miller-Abbott Tube, *New England J. Med.* **225**:641, 1941.

216. Blodgett, J. B.: An Evaluation of Intestinal Suction in Intestinal Obstruction, *Surgery* **11**:739, 1942.

Such a possibility is carefully considered by Abbott and Holden <sup>217</sup> in a discussion of hypoprothrombinemia in intestinal disorders.

*Parasitic Diseases.*—With the existence of global war there can be no doubt that civilian, as well as military, physicians will be confronted with many hitherto more or less neglected disease conditions. A closer association with foreign populations, particularly in the tropics, will automatically make possible the transfer of so-called "tropical diseases" to more temperate climates. The prevalence of amebiasis in this country is generally recognized, but its actual incidence is not fully appreciated by physicians practicing in the more northern sections of the country. For this reason an article by Faust <sup>218</sup> on the prevalence of amebiasis in the western hemisphere is extremely timely and should be perused with a great deal of care. In spite of the discrepancies among various surveys already made in different parts of the country, many of which are too fragmentary or too limited in scope to provide an adequate basis for conclusions, Faust believes that amebiasis exists in an appreciable portion of the population of the western hemisphere from central west Canada to the Strait of Magellan. He feels certain that it is much more intensely endemic in the American tropics than in the temperate zones but makes the rather astounding estimate that in areas like the United States the incidence may average as high as 20 per cent, a figure possibly double that previously accepted. Evidence that such an estimate is not overdrawn may be found, for example, in an article on amebiasis in the Yakima Valley, Wash., by Lewis and Low.<sup>219</sup> Examination of a large number of stools over a period of five years revealed that amebas could be demonstrated in 21.5 per cent of 586 specimens, and of these, *Endamoeba histolytica* accounted for more than half. The unusually large number of Orientals inhabiting the Yakima Valley is a contributing factor, and the authors make a pertinent observation when they mention that purification of water by the chlorination-sedimentation method is ineffective against contamination by amebic cysts.

It is generally accepted that subclinical infection in human beings caused by *Trichinella spiralis* is extremely common, and a recent report by Most and Helpern,<sup>220</sup> who used the most careful digestion, press and microscopic methods, revealed that 22 per cent of 100 persons dying by violence in New York city showed evidence of human trichinosis.

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217. Abbott, W. E., and Holden, W. D.: Hypoprothrombinemia in Intestinal Disorders, *Am. J. Surg.* **53**:215, 1941.

218. Faust, E. C.: The Prevalence of Amebiasis in the Western Hemisphere, *Am. J. Trop. Med.* **22**:93, 1942.

219. Lewis, P. J., and Low, J. H.: Amebiasis in Yakima Valley, Northwest Med. **41**:52, 1942.

220. Most, H., and Helpern, M.: Incidence of Trichinosis in New York City, *Am. J. M. Sc.* **202**:251, 1941.

Wyrens, Tillisch and Magath <sup>221</sup> add still another report to those already extant. Theirs is of interest for the fact that in 21 of 40 cases mentioned the diagnosis was made incidentally during routine examination of surgical pathologic material, the parasites being found in specimens of muscle removed from various parts of the body, in tonsillar and in thyroid tissue and in tissue removed from the lips. In the other 19 cases clinical trichinosis was present.

The treatment of various parasitic diseases is well considered in the newer textbooks on the subjects. An excellent summary, however, is presented in adequate detail and in convenient form by Faust <sup>222</sup> in an article entitled "The Chemotherapy of Intestinal Parasites," in which he discusses the most recent and successful forms of treatment. The author takes up in order the use of emetine, chiniofon powder, diodoquin (5,7-diiodo-8-hydroxyquinoline) and carbarsone in the treatment of amebiasis, atabrine in giardiasis and gentian violet in infections caused by *Oxyuris* and *Strongyloides*; hexylresorcinol is advocated in the treatment of ascariasis; for hookworm infection the author routinely uses tetrachlorethylene and (or) hexylresorcinol; for infection caused by whipworm no specific drug therapy is available, but the use of fresh crude latex and the repeated administration of tetrachlorethylene are mentioned; infection caused by tapeworm may be treated successfully either by oleoresin of aspidium or by carbon tetrachloride. The article is written in enough detail that it is highly informative. Manson-Bahr <sup>223</sup> believes that the most effective treatment for amebiasis is a combined method of therapy, consisting of quinoxyl (a mixture of iodo-hydroxyquinoline sulfonic acid and bicarbonate of soda) retention enemas by day and administration of emetine bismuth iodide by night. Using this method, the author had a relapse rate of only 3.7 per cent in 361 patients. Kuitunen-Ekbaum <sup>224</sup> has found that phenothiazine is extremely efficacious in the treatment of infection caused by pinworm and claims complete cures in 84 of 98 cases by the first course of treatment. Although it is generally recognized that giardiasis may be successfully treated by atabrine, there is still a reasonably skeptical attitude toward the relation that infections caused by *Giardia* bear to the production of symptoms. For this reason, it is of some interest to learn from an article by Hartman

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221. Wyrens, R. G.; Tillisch, J. H., and Magath, T. B.: Trichinosis: Report of Nineteen Cases of Clinical Infection and Twenty-One Cases of Asymptomatic Infection, *J. A. M. A.* **117**:428 (Aug. 9) 1941.

222. Faust, E. C.: Chemotherapy of Intestinal Parasities, *J. A. M. A.* **117**: 1331 (Oct. 18) 1941.

223. Manson-Bahr, P.: Amebic Dysentery and Its Effective Treatment; Critical Study of Five Hundred and Thirty-Five Cases, *Brit. M. J.* **2**:255, 1941.

224. Kuitunen-Ekbaum, E.: Phenothiazine in the Treatment of Enterobiasis, *Canad. Pub. Health J.* **32**:308, 1941.



and Kyser<sup>225</sup> that apparently atabrine therapy completely relieved the rather indefinite symptoms presented by a group of patients in whom the demonstration of giardias in the intestine was the only positive clinical finding.

*Specific Infections, Diagnosis and Treatment.*—An apparently unique case of multiple subserous abscesses in a single locality of the stomach wall is described by Sauer and Lisa.<sup>226</sup> The report is mentioned, in spite of the fact that the causation remained obscure, because there appears to be no report of a similar condition in the literature. Histologic studies revealed chronic gastritis and multiple acute subserous abscesses.

Infections caused by Welch's bacillus have rarely given rise to serious lesions in the stomach and the duodenum. Only 12 cases were found in the literature by Quinn and his colleagues.<sup>227</sup> They add 2 new cases, in which localized infection due solely to Welch's bacillus was encountered in the stomach and the duodenum. Recovery was reported in only 1 case.

Because of the increasing tendency to segregate patients suffering from tuberculosis in special institutions it is an unfortunate fact that younger physicians are becoming less familiar with the various manifestations of this disease. For this reason reference to current articles should be of interest. Burke and Aronovitch<sup>228</sup> comment on the incidence of ulcerative intestinal tuberculosis encountered among patients in a sanatorium. Of 99 consecutive autopsies, ulcerative lesions in the digestive tract were encountered in 70 per cent. Over a period of fourteen months 226 patients in the same institution revealed an incidence of intestinal tuberculosis of 31.4 per cent when examined by a method previously described by Brown and Sampson. Because of the histories of dietary inadequacy obtained from a large number of these patients, vitamin therapy was instituted in the hospital, with particular attention to vitamins C and D. It is the authors' impression that there has been a marked decrease in the number of patients presenting symptoms referable to the intestinal tract since the beginning of such therapy. It would be of interest to know whether during this period patients with less advanced tuberculous conditions were being admitted than in former years. Such a possibility might in part explain the apparent improvement in therapeutic results. It is of incidental interest that in children, at any rate.

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225. Hartman, H. R., and Kyser, F. A.: Giardiasis and Its Treatment, *J. A. M. A.* **116**:2835 (June 28) 1941.

226. Sauer, P. K., and Lisa, J. R.: Abscess of the Stomach Wall: Report of a Case, *Surgery* **10**:899, 1941.

227. Quinn, W. C.; Lord, J. W., Jr., and Wade, L. J.: Welch Bacillus Infections Arising from the Stomach and Duodenum, *Surgery* **11**:229, 1942.

228. Burke, H. E., and Aronovitch, M.: Intestinal Tuberculosis, *Canad. M. A. J.* **45**:21, 1941.

gastric lavage may be an important procedure in the diagnosis of tuberculosis. Davies and Doherty<sup>229</sup> surveyed the results of examination of gastric contents in 75 boys and girls ranging from 2 to 11 years of age. Of this group, 64 children had pulmonary tuberculosis and 11 had non-pulmonary lesions. Tubercle bacilli of the type causing tuberculosis in human beings were present in the gastric contents of 24 of the patients with pulmonary tuberculosis but not in those of any children suffering from nonpulmonary lesions. Although such a maneuver is rarely necessary or indicated in adults, it undoubtedly is occasionally indicated in children, in whom the obtaining of satisfactory specimens of sputum is often difficult. The possible importance of abdominal tuberculosis in causing symptoms in children leading to erroneous diagnoses is stressed in an article by Harrenstein.<sup>230</sup> Under the term abdominal tuberculosis this author includes involvement of the peritoneum and tuberculosis of the mesenteric lymph nodes and of the abdominal organs. The slight cutaneous sensitivity to tuberculin of patients with these conditions increases the diagnostic difficulties. In 47 of 48 children the cause of symptoms was established only by operation. The first diagnosis for the majority of the children had been erroneous, the tuberculous process being frequently mistaken for appendicitis. In 20 children active tuberculosis of the lymphatic nodes was encountered; in 23 tuberculous peritonitis was encountered, and in 5 intestinal lesions were suspected. Because of the probability of an increase in the morbidity from tuberculosis due to war or postwar conditions, articles on this disease are of current interest.

A rather unusual manifestation of early syphilis of the stomach is reported by Reynolds,<sup>231</sup> who relates the case of a 34 year old Negro with pyloric obstruction. The patient was found to have a chronic interstitial inflammatory lesion of the wall of the stomach associated with early syphilis. That the syphilitic infection was recent seemed clear because of the presence of a penile lesion and a characteristic plantar syphilid with generalized lymphadenopathy. That the gastric lesion was also due to syphilis seemed entirely probable because of the suggestive histopathologic data and the response to specific treatment. Another rare manifestation of syphilis of the digestive tract is to be found in a case report of Hernández-Morales and Ruiz-Cestero,<sup>232</sup> who describe a case

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229. Davies, T. W., and Doherty, C. J.: Gastric Lavage in Diagnosis of Tuberculosis in Children: Survey of Seventy-Five Cases, *Brit. M. J.* **1**:212, 1942.

230. Harrenstein, R. J.: Abdominal Tuberculosis in Children, *Maandschr. v. kindergeneesk.* **9**:442, 1940.

231. Reynolds, F. W.: Gastric Lesions Associated with Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:218, 1942.

232. Hernández-Morales, F., and Ruiz-Cestero, G.: Syphilis of the Duodenum, *Am. J. Digest. Dis.* **8**:302, 1941.

in which an obstructing lesion in the second portion of the duodenum responded slowly to antisyphilitic treatment; there was also serologic evidence of the disease. Proof of healing was obtained by repeated roentgen examination, as well as by the disappearance of symptoms.

Actinomycosis of the gastrointestinal tract is sufficiently rare to warrant including a report by Woodman<sup>233</sup> of a case in which the condition was diagnosed at operation. Involvement of the cecum, ascending colon and liver was demonstrated, in addition to multiple small pulmonary abscesses.

Recent improvements in the diagnosis and treatment of bacillary dysentery are of immediate interest because of the obviously increased exposure to this infection of a large number of American troops and civilians moving to different parts of the world. The fairly recent development of a culture medium selective for *Bacillus dysenteriae* (Flexner) is reported by Wilson and Blair.<sup>234</sup> They have found that lactose nutrient agar containing optimum amounts of potassium tellurite, potassium ferric iron and rosolic acid provides a medium on which Flexner's organisms grow profusely, whereas the growth of most strains of *Escherichia coli* and *Bacillus lactis aerogenes* is inhibited. The growth of salmonellas which cause food poisoning, typhoid and paratyphoid bacilli, Sonne's dysentery bacillus and cholera vibrios is suppressed. A careful clinicopathologic study of 263 consecutive cases of acute bacillary dysentery observed in the Canal Zone is presented by Macumber.<sup>235</sup> The organisms recovered from stools consisted entirely of members of the Flexner and the Sonne group, those of the former predominating heavily. No case of infection with Shiga's bacillus was encountered. By means of control cases Macumber concludes that no evidence could be obtained indicating that polyvalent serum therapy was of value. The mortality for the entire series was 6.5 per cent, relatively more deaths being due to infections caused by Sonne's bacillus. Careful microscopic studies were made of the pathologic material obtained in 13 cases. The results of these are given in detail. This report is of particular interest inasmuch as the mortality figures are based on the results of treatment before the use of chemotherapeutic agents. A report from the Netherlands East Indies is of interest. Esseveld and his colleagues<sup>236</sup> studied 64 cases of mild

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233. Woodman, T. W.: Abdominal Actinomycosis, *Southwestern Med.* **25**: 81, 1941.

234. Wilson, W. J., and Blair, E. M. M.: Tellurite-Iron Rosolic Acid Medium Selective for *Bacillus Dysenteriae* (Flexner), *Brit. M. J.* **2**:501, 1941.

235. Macumber, H. H.: Acute Bacillary Dysentery: A Clinicopathologic Study of Two Hundred and Sixty-Three Consecutive Cases, *Arch. Int. Med.* **69**: 624 (April) 1942.

236. Esseveld, H.; Beau, W., and Boars, J. K.: Bacteria of Newcastle Dysentery Group from Feces of Patients with Symptomatology and Bacillary Dysentery in Netherlands East Indies, *Geneesk. tijdschr. v. Nederl.-Indië* **81**:2622, 1941.

dysentery on the east coast of Sumatra. The feces yielded a bacterial strain of the Manchester type of the Newcastle dysentery organisms. Simultaneous bacteriologic tests on the feces from patients without dysentery never disclosed this strain. A report from Germany by Roelcke and Neuberger<sup>237</sup> was received in 1941 in which the authors maintained that the Kruse-Sonne form of dysentery has shown a considerable increase in the past ten years. Infection caused by Shiga-Kruse bacilli was never detected, and the authors claim that in recent years Kruse-Sonne bacilli account for over 85 per cent of all cases of dysentery in Germany. The highest incidence was observed in children under 10 years of age and occurred during the summer months. Kruse-Sonne dysentery occurred as frequently as infection caused by paratyphoid B organisms. A most unusual clinical manifestation of bacillary dysentery is described in a report by Thorne and Estabrook.<sup>238</sup> A major outbreak of diarrheal disease and infectious jaundice occurred in a Vermont state school, an institution with a capacity of three hundred and eighty beds. During a ten month period there were three distinct phases, which occurred as follows: Thirty-two patients showed symptoms of dysentery alone during the first phase of the epidemic; 26 patients showed dysentery and jaundice later, and subsequently 62 patients presented jaundice alone. Flexner's organisms were demonstrated in 50 patients having dysentery alone, in 2 patients presenting dysentery and jaundice together and in 5 patients presenting jaundice alone. The organisms were also found in 14 symptom-free carriers and were demonstrable in stool specimens intermittently for weeks or months after the end of the acute epidemic. The authors are careful to avoid drawing any conclusions as to the relation between the jaundice and the infection with dysentery bacilli, which were probably introduced by a symptom-free carrier and spread by improperly disinfected clothing passing through a central laundry.

Therapeutic measures to be considered in the treatment of bacillary dysentery at present include serum therapy and the use of bacteriophages and various chemotherapeutic agents. A comment has already been made on what appear to be carefully controlled reports following the use of polyvalent antiserum. The use of dysentery bacteriophages is discussed by Klieve and Helmreich<sup>239</sup> and by Soesman.<sup>240</sup> The former article

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237. Roelcke, K., and Neuberger, M.: Statistics on Kruse-Sonne (E) Dysentery: The Infectious Intestinal Disease Most Prevalent in Germany, München. med. Wchnschr. **88**:643, 1941.

238. Thorne, F. C., and Estabrook, J. S.: The Association of Bacillary Dysentery and Infectious Jaundice, J. A. M. A. **117**:89 (July 12) 1941.

239. Klieve, H., and Helmreich, W.: Dysentery Bacteriophages, München. med. Wchnschr. **88**:617, 1941.

240. Soesman, J.: Polybacteriophage in Treatment of Bacillary Dysentery, Geneesk. tijdschr. v. Nederl.-Indië **81**:1863, 1941.

reports the results obtained by German physicians in Poland. These authors believe that opinions about the value of bacteriophages in the treatment of dysentery are divided because the bacteriophages differ in efficacy. It has been found that not only the bacilli vary in different epidemics and endemic foci but probably the bacteriophages. In Poland the authors observed that local strains of bacteriophage produced lysis in all strains of dysentery bacilli obtained locally, whereas bacteriophages brought in from Germany did not. They believe it highly important to use a potent polyvalent mixture produced from locally obtained strains. The prophylactic value of their bacteriophage mixture was tested, and it was noted that in the course of eight weeks following the administration of the mixture, dysentery developed in 10 of 250 controls, whereas not a single man of the 113 who had received prophylactic treatment had the disease. During the course of an epidemic it was proved that bacteriophage therapy was effective in cases of mild or moderately severe infection caused by Flexner Y organisms. The treatment was not so effective in the cases of most severe infection. It is of interest that apparently the administration of bacteriophage was successful in the treatment of carriers. Similar results appear to have been obtained by Soesman, who treated 50 patients with bacillary dysentery with polyvalent bacteriophage during an epidemic in the Netherlands East Indies. The author considered that in most instances severe symptoms disappeared more rapidly than in untreated patients. All of the patients in this group recovered.

The use of sulfonamide compounds in the treatment of intestinal infections was to have been expected and has already been productive of important results. Of the various preparations, sulfaguanidine (sulfanilylguanidine) has received the most attention, inasmuch as it was hoped originally that the action of this drug would be largely confined to the intestinal tract. According to the original report of Marshall and his collaborators (1940), the drug in mice and dogs is poorly absorbed from the intestinal tract, and subsequent studies by Corwin<sup>241</sup> substantiate this result in the case of dogs and monkeys. A species difference definitely exists, however, and later reports indicate that an appreciable amount of the drug is absorbed in human beings and may, at times, produce toxic symptoms. Such a discrepancy is noted, for example, in the report of Beling and Abel,<sup>242</sup> who demonstrated urinary excretion of sulfaguanidine by human beings in amounts ranging from 29 to 66 per cent of a total ingested dose with the exception of 1 subject who excreted 96 per cent of the drug. The authors are agreed that the compound is effective in reducing the total number of colon bacilli in the stools,

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241. Corwin, W. C.: Studies on the Chronic Toxicity of Sulfaguanidine (Sulfanilylguanidine), *Bull. Johns Hopkins Hosp.* **69**:39, 1941.

242. Beling, C. A., and Abel, A. R.: Sulfaguanidine: Absorption, Excretion and Therapy, *J. M. Soc. New Jersey* **38**:629, 1941.

although the growth of anaerobic bacteria is not influenced. Corwin, among others, noted that the drug did not cause a decrease in the total number of organisms, although it caused a marked suppression of gram-negative bacilli and permitted a concomitant increase in gram-positive cocci. In animal experiments Bloomfield and Lew<sup>243</sup> showed that the drug, even when administered in small doses, had a striking prophylactic effect against the spontaneous development of ulcerative cecitis in rats, at the same time preventing any loss of weight, although the disease developed in untreated rats and the animals showed evidence of profound nutritional disturbances. These authors suggest the trial of this or similar drugs as a prophylactic measure in military establishments. Comparative studies on the effects of sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfaguanidine were made by Lawrence and Sprague,<sup>244</sup> who used these drugs to determine in animals their effect against colon-typhoid-dysentery organisms. Feeding the several compounds in the diet to mice caused with a single exception a significant reduction in the number of coliform organisms normally present in the intestinal contents; sulfanilamide apparently had no effect. From Mexico comes a report by Aquilar<sup>245</sup> on the use of sulfapyridine in the treatment of mucosanguineous colitis. This author reports excellent results following the administration of sulfapyridine in some 200 cases. Keeley and McCord<sup>246</sup> investigated the absorption of sulfaguanidine from the colon after administering it through well functioning colostomy openings. The authors conclude that the drug in the form of an aqueous suspension when introduced directly into the large bowel through a colostomy stoma is not absorbed from the left half of the colon in human beings.

The therapeutic trial of sulfonamide compounds in acute intestinal infections is reported by various writers. Valdès and Sosa-Gallardo<sup>247</sup> employed sulfathiazole in the treatment of 43 children with bacillary dysentery (17 with Shiga dysentery, 6 with Flexner dysentery and 20

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243. Bloomfield, A. L., and Lew, W.: Prophylactic Effect of Sulfaguanidine Against Ulcerative Cecitis in Rats, *Proc. Soc. Exper. Biol. & Med.* **48**:363, 1941.

244. Lawrence, C. A., and Sprague, K. D.: Effects of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfanilylguanidine upon Colon-Typhoid-Dysentery Group, *Proc. Soc. Exper. Biol. & Med.* **48**:696, 1941.

245. Aquilar, R.: Sulfapyridine in Therapy of Mucosanguineous Colitis, *Rev. méd. d. Hosp. gen.* **3**:504, 1941.

246. Keeley, J. L., and McCord, W. M.: Concentration of Sulfaguanidine (Sulfanilylguanidine) in the Peripheral Blood of Human Beings After Its Introduction into the Large Bowel and After Oral Administration, *J. Lab. & Clin. Med.* **27**:785, 1942.

247. Valdès, J. M., and Sosa-Gallardo, J. B.: Treatment of Bacillary Dysentery with Sulfathiazole, *Arch. argent. de pediat.* **17**:3, 1942.

with Sonne dysentery). There were no deaths, and tenesmus, colic and other disturbances disappeared within six to eight hours after ingestion of the drug. The number of evacuations decreased and became normal before seventy-two hours had elapsed. The authors gained the impression that infectious diarrhea which proved refractory to sulfathiazole should be considered of nondysenteric origin. A report from Cooper and his associates<sup>248</sup> presents the results of sulfathiazole treatment of acute diarrhea in 123 infants and children. An analysis of the results showed that the drug was of therapeutic value in patients whose stools were positive for *Shigella paradysenteriae* but was without demonstrable effect in the treatment of patients whose stools were negative for this organism. The data indicated that sulfathiazole hastened the disappearance of *S. paradysenteriae* from the stools of the treated patients. Seventeen of 34 patients who did not receive sulfathiazole had cultures of stools which were positive for these organisms on discharge from the hospital, while only 1 of 17 patients treated with the drug had cultures which were thus positive at the time of discharge. A careful control experiment was carried out by Anderson, Cruickshank and Walker,<sup>249</sup> who administered sulfaguanidine to alternate patients suffering from attacks of Flexner dysentery. Of the total of 96 patients, 41 received the drug and 55 were untreated controls. The results on the drug-treated patients were excellent. In a case of typical severe dysentery thus treated the patient's condition improved in twenty-four hours after receiving the drug, and by the thirteenth day practically all symptoms had disappeared. Bowel movements were much less frequent within two days, although blood and mucus often persisted in the stools for three or four days. Convalescence was much shorter than in the untreated patients, and treatment with the drug in the acute stage apparently prevented the convalescent carrier state, which was present in about half of the untreated patients. A smaller but similar control experiment was carried out by Hall<sup>250</sup> on 30 patients suffering from dysentery due without exception to Hiss Y bacilli. Of the 30 patients, all but 5 were infants or children. The results on the drug-treated patients were excellent, and all but 2 had a dramatic response in about twenty-four hours. In the control group the course of the disease followed that which had been observed in the past, and there was 1 death. In the same report the authors record the effects of a similar course of treatment in

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248. Cooper, M. L.; Zucker, R. L., and Wagoner, S., with statistical analysis by Brown, E. W., and Bennett, R.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children, *J. A. M. A.* **117**:1520 (Nov. 1) 1941.

249. Anderson, D. E. W.; Cruickshank, R., and Walker, J.: Treatment of Bacillary (Flexner) Dysentery with Sulfanilylguanidine, *Brit. M. J.* **2**:497, 1941.

250. Hall, L. C.: The Use of Sulfaguanidine in Enteric Infections, *J. Pediat.* **20**:328, 1942.

5 patients with infection caused by typhoid organisms. In this group apparently the drug was completely ineffective, a result which has been observed by all other investigators. Of particular importance in the present war emergency is the report of Rantz and Kirby,<sup>251</sup> who observed the results following sulfaguanidine therapy in the treatment of dysentery carriers. Eleven carriers, picked up in a recent survey in San Francisco, were treated with an average dose of 50 Gm. administered over two to six days. In 9 of the 11 persons dysentery bacilli disappeared from the stools during treatment and could not be demonstrated in subsequent periods of study varying from thirty to ninety days. In 2 instances the treatment appeared to be ineffective even after three courses of therapy. It is important to note that all of the patients remained ambulatory and continued to work while being treated.

The newest member of the sulfonamide compounds to be utilized in the treatment of intestinal infection is sulfasuxidine (succinyl-sulfathiazole). Thorough pharmacologic studies by Miller and associates<sup>252</sup> have demonstrated that succinylsulfathiazole administered orally to dogs has little toxicity; that it is poorly absorbed from the intestinal tract, so that only an average of about 5 per cent or less of the ingested drug is excreted by the kidneys; that its action is essentially in the intestinal tract, affecting principally the contents of the bowel; that it has a marked effect in altering the bacterial flora, as demonstrated by the reduction in the count of *E. coli* and related organisms, and that in therapeutic doses it profoundly alters the feces, which become semifluid and practically odorless. It has also been observed that dysentery bacilli, including Shiga, Flexner and Sonne strains, are susceptible to its antibacterial action, and the fact that the feces become relatively odorless indicates marked inhibition of anaerobic proteolytic bacteria. Reports by Poth and his collaborators<sup>253</sup> form the basis for such conclusions. These authors have used as a preliminary working dose in human beings 0.25 Gm. per kilogram per day administered orally. They

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251. Rantz, L. A., and Kirby, W. M. M.: The Use of Sulfaguanidine in the Treatment of Dysentery Carriers, *J. A. M. A.* **118**:1268 (April 11) 1942.

252. Miller, E.; Rock, H. J., and Moore, M. L.: Substituted Sulfanilamide: I. N<sup>4</sup>-Acyl Derivative, *J. Am. Chem. Soc.* **61**:1198, 1939. Moore, M. L.; Miller, C. S., and Miller, E.: Substituted Sulfanilamide: II. N<sup>4</sup>-Acyl-N<sup>1</sup>-Hydroxyl Derivative, *ibid.* **62**:2097, 1940. Moore, M. L., and Miller, C. S.: Dicarboxylic Acid Derivatives of Sulfonamide, *ibid.* **64**:1572, 1942.

253. Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Clinicotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Arch. Surg.* **44**:187 (Feb.) 1942. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, *ibid.* **44**:208 (Feb.) 1942; Succinyl Sulfathiazole: A New Bacteriostatic Agent Locally Active in the Gastro-Intestinal Tract, *Proc. Soc. Exper. Biol. & Med.* **48**:129, 1941.



have found that there is a significant lowering of the coliform organisms in 90 per cent of instances after the administration of the drug in adequate doses. The medication has been effective in the presence of extensive ulcerating lesions of the bowel, and they suggest the administration of succinylsulfathiazole for the preoperative preparation of patients requiring surgical procedures on the gastrointestinal tract and for the treatment of acute intestinal infections, such as typhoid fever and dysentery. All the evidence at hand seems to indicate that the action of the drug is limited essentially to its local effect on the contents of the gastrointestinal tract. Such has been the experience of various investigators, including my own. From unpublished data it appears that the drug is of no value in the treatment of typhoid fever, as is shown by Kirby and Rantz.<sup>254</sup> These authors administered the drug to normal persons and to typhoid and to dysentery carriers, and the results are compared to those following the administration of sulfaguanidine. Succinylsulfathiazole was given to 11 persons in the dose suggested by Poth and associates in the articles just referred to. Three of the subjects were apparently normal; 3 were typhoid carriers, and 5 were dysentery carriers. Although the drug produced a decided alteration of physical characteristics in the bacterial flora of the stools, typhoid bacilli remained viable in the stools of the 3 carriers during two weeks of drug therapy. In the case of dysentery carriers the bacilli disappeared from the stools during the administration of the drug and remained absent for periods varying from thirty to sixty days. It would appear that this new drug, which is now available, offers a distinct advantage in the treatment of many acute intestinal infections, particularly those due to the dysentery-like bacilli. Further reports on its effectiveness should receive careful scrutiny. Because of the minimal amount of absorption from the gastrointestinal tract, its use should be associated with few toxic symptoms, and for this reason it should prove preferable to sulfaguanidine.

The treatment of lymphogranuloma venereum by sulfonamide compounds is considered by Palmer, Kirsner and Rodaniche.<sup>255</sup> In addition to an excellent discussion of the disease in the clinical and the subclinical form, the authors present their impression of the results of chemotherapy. They believe that treatment with sulfanilamide and sulfaguanidine is of definite value, particularly in those cases in which there is no stricture formation, but warn that prolonged administration of the drugs may

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254. Kirby, W. M. M., and Rantz, L. A.: *The Treatment of Typhoid and Dysentery Carriers with Succinylsulfathiazole*, J. A. M. A. **119**:615 (June 20) 1942.

255. Palmer, W. L.; Kirsner, J. B., and Rodaniche, E. C.: *Studies on Lymphogranuloma Venereum Infection of the Rectum*, J. A. M. A. **118**:517 (Feb. 14) 1942.

be necessary. On the basis of experimental and clinical evidence they conclude that the sulfonamide compounds are unable to destroy all the virus in the body but that they do tend to inhibit its action. Six patients suffering from proctitis due to lymphogranuloma venereum were treated with sulfaguanidine by Cañizares and Morris.<sup>256</sup> Their results coincided with the impressions gained by Palmer and his associates. Those patients with simple inflammatory proctitis experienced subjective and objective improvement, which was not noted in the patients with narrow fibrotic strictures. Such a result is not surprising and serves to indicate the wisdom of early diagnosis and treatment of this not uncommon condition before rectal strictures develop.

Continued studies reveal the great importance of stools as a source of infection in poliomyelitis. One of the latest reports is that of McClure,<sup>257</sup> who was able to obtain five "takes" after inoculation of monkeys with material obtained from stools of 17 patients with typical, abortive or atypical suspected poliomyelitis. All of the successful passages were from stools of infants under 2 years of age. No answer has yet been obtained to the question as to what conditions are necessary for the poliomyelitis virus to remain infectious in stools. As a public health measure the subject warrants prolonged and thorough investigation.

A rather unusual report having to do with the bacterial flora of the intestinal tract is contained in an article by Bergeim and his colleagues,<sup>258</sup> who noted that there was a 57 per cent recovery of *Bacillus prodigiosus* from the large intestine in man when such bacteria were ingested with a given amount of olive oil. Only 11 per cent recovery was obtained when the bacteria were ingested with butter fat and less than 2 per cent when taken with an equal amount of an alcoholic extract of butter fat with a higher butyrate content. Concentrations of butyric acid inhibiting growth or killing bacteria at different  $p_H$  values are reported for about twenty organisms, including many which occur normally or pathologically in the intestine. Such studies may indicate a further method of possible therapeutic control of the intestinal flora. In a somewhat similar form of study Portis and Fishbein<sup>259</sup> noted that

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256 Cañizares, O., and Morris, G. E.: Sulfaguanidine in Treatment of Proctitis Due to Lymphogranuloma Venereum: Report of Six Cases, *Arch. Dermat. & Syph.* **44**:873 (Dec.) 1941.

257. McClure, G. Y.: High Incidence of Infective Stools in a Small Outbreak of Infantile Paralysis, *J. Lab. & Clin. Med.* **27**:1906, 1941.

258. Bergeim, O.; Hanszen, A. H.; Pincussen, L., and Weiss, E.: Relation of Volatile Fatty Acids and Hydrogen Sulphide to the Intestinal Flora, *J. Infect. Dis.* **69**:155, 1941.

259. Portis, S. A., and Fishbein, W. I.: Studies of Feces and Clinical Conditions Following Ingestion of Grape Juice, *Illinois M. J.* **80**:336, 1941.

the ingestion of 24 ounces (720 cc.) of grape juice daily increased the number of gram-positive organisms in the stools in a consistent fashion, along with the acidophilus bacilli. The effect of the continued use of this preparation in 50 persons who tended to complain of chronic constipation was striking. No laxatives were needed throughout the course of the experiment.

An excellent example of an epidemiologic study of an outbreak of food poisoning is given by Kleeman and his associates.<sup>260</sup> Two cases of food poisoning were found to be due to smoked fish, the source of which was eventually traced and eradicated. Samples of the food gave high counts of *Proteus vulgaris*. The principal importance of the article lies in the attention that it draws to the hazards concerned in the distribution of perishable foods, such as fish.

An explanation of the favorable effect of pectin on infectious diarrheas caused by intestinal pathogens is the subject of a report by Werch and associates<sup>261</sup> following studies on various intestinal pathogens, such as the typhoid-dysentery group. The authors present evidence, which seems reasonably convincing, that pectin, galacturonic acid and their decomposition products manifest bactericidal, as well as bacteriostatic, activity. They believe that the influence of pectin on the  $p_H$  of the intestinal contents is the most probable explanation of its antibacterial activity.

*Regional Enteritis.*—Although the cause of regional enteritis still remains an unknown quantity, continued clinical investigations bring into clearer relief the various manifestations of this unusual disease. A report by Wirts and Lyon<sup>262</sup> on 71 cases encountered at six teaching hospitals in Philadelphia constitutes a satisfactory summary of clinical knowledge of the condition at the present time. In all cases the patients had been operated on. Of 27 considered to have the advanced form of the disease, one third had had appendectomies at an average time of twenty months prior to the major operation. The remaining 44 patients were considered to have had an early form of the disease, and the majority in this group before operation had conditions given the diagnosis of acute appendicitis. A resemblance to the last-named disorder seems to be one of the most typical characteristics of the condition, and

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260. Kleeman, I.; Frant, S., and Abrahamson, A. E.: Food Poisoning Outbreaks Involving Smoked Fish: Their Epidemiology and Control, *Am. J. Pub. Health* **32**:151, 1942.

261. Werch, S. C.; Jung, R. W.; Plenk, H.; Day, A. A., and Ivy, A. C.: Pectin and Galacturonic Acid and the Intestinal Pathogens, *Am. J. Dis. Child.* **63**:839 (May) 1942.

262. Wirts, C. W., Jr., and Lyon, B. B. V.: The Incidence of Regional Ileitis, *Am. J. Digest. Dis.* **8**:246, 1941.

the confusion in diagnosis illustrates the difficulty with which the early stages of the condition are recognized. The authors have collected 17 other cases, in which the evidence was not sufficiently complete to warrant an absolute diagnosis of regional enteritis. In these cases the patients were not operated on, although the diagnosis was reasonably certain on the basis of signs, symptoms and laboratory studies. Partial or complete relief of symptoms in this group was obtained in essentially one half of the patients, who were maintained on a medical regimen. The authors conclude that it is highly probable that the early form of the disease does not necessarily progress to the advanced state. Certainly, a review of the available literature indicates that in a fair number of patients immediate radical surgical intervention is not warranted, even in the presence of an adequate diagnosis and that conservative measures are still justified in the absence of any exact knowledge as to the cause of the disease. Such conservative measures, however, are justified only in those instances in which it is possible to maintain a constant watch over the individual patient. Brown and Donald,<sup>263</sup> on the contrary, believe that in every case surgical removal of the diseased segment of bowel is indicated, and there can be no doubt that the characteristic course of the condition, with its remissions and exacerbations similar to those encountered among patients with peptic ulcer and chronic ulcerative colitis, cannot be forgotten. In the report of these authors on 178 patients one again finds an excellent summary of the present information concerning the disease, including comments on its incidence, the distribution of its lesions and its progress. One important therapeutic note in this report is the statement by Brown and Donald that the most important feature in the postoperative care of the condition is the maintenance of a high protein diet which is supplemented with the vitamin B complex. There can be no doubt that this is a most important consideration, and too frequently the necessity of carrying out careful nutritional therapy after the removal of an appreciable amount of the absorptive surface of the small bowel is not observed, with resulting disability and occasionally the development of serious nutritional disorders.

It is not too common to encounter massive hemorrhage in association with regional enteritis. Fallis<sup>264</sup> reports 1 case of such an occurrence, the only one in a group of 27 patients in whom operation was performed because of repeated and profuse intestinal bleeding. The condition was not suspected until a laparotomy was performed.

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263. Brown, P. W., and Donald, D. J., Jr.: Prognosis of Regional Enteritis, *Am. J. Digest. Dis.* 9:87, 1942.

264. Fallis, L. S.: Massive Intestinal Hemorrhage in Regional Enteritis: Report of a Case, *Am. J. Surg.* 53:512, 1941.

One set of experiments by Poppe<sup>265</sup> has more or less succeeded in reproducing some of the features of enteritis and is quite similar to some other experiments carried out within recent years. In dogs the author was able to produce acute and chronic enteritis, with some additional involvement of the colonic mucosa, by obstructing the lymphatic drainage of the ileocecal segment of the intestine. Ulcerating lesions could be produced without the injection of any bacteria, but the injection of non-pathogenic bacteria into the mesenteric lymph nodes appeared to produce acute, generalized enteritis, rather than the chronic ulcerating form. Such experiments suggest the possible mechanism underlying the production of regional enteritis but unfortunately do not contribute any definite evidence of its causation.

*Nonspecific Ulcerative Colitis.*—The question of the causation, diagnosis and treatment of chronic ulcerative colitis continues to be the basis of investigation and speculation. Various diagnostic methods are well discussed by Paulson.<sup>266</sup> In his critical analysis of the various procedures he stresses the need for complete studies, including a search for specific micro-organisms, parasites and viruses. The seriousness of ulcerative colitis is such that a perusal of Paulson's article is worth while, largely because it presents all of the various aids that may be utilized from time to time in evaluating a given case.

The frequency with which this disease may be encountered in young children is not generally recognized. For this reason the report by Elitzak and Widerman<sup>267</sup> should be mentioned. Twenty-seven patients were observed in an age group ranging from two weeks upward. Eight of the patients died, and most of the fatalities occurred in infants under the age of 1 year, the duration of the disease in these patients varying from six days to one year. In 5 of the surviving patients the disease showed no symptoms of activity for a long time and the lesions seemed to be healed. In spite of this small group of cases of apparently arrested disease the authors properly point out that the prognosis must be guarded because of the characteristic tendency toward relapses and recurrences. Occasional instances are reported of a familial occurrence of the condition. Jackman<sup>268</sup> in a review of 900 cases found that less than 2 per

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265. Poppe, J. K.: Reproduction of Ulcerative Colitis in Dogs, *Arch. Surg.* **43**:551 (Oct.) 1941.

266. Paulson, M.: Diagnostic Methods in Chronic Ulcerative Colitis: A Critical Analysis of Procedures Used in the Differential Diagnosis of the Diarrheas and Dysenteries, *Am. J. Clin. Path.* **11**:588, 1941.

267. Elitzak, J., and Widerman, A. H.: Nonspecific Ulcerative Colitis in Childhood, *Am. J. Dis. Child.* **62**:115 (July) 1941.

268. Jackman, R. J.: Familial Occurrence of Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis): Report of Case, *Proc. Staff Meet., Mayo Clin.* **17**:154, 1942.

cent were encountered in which 2 or more members of a family had the disease. Detailed reports are given by him on 2 families, which are of some interest. In the first family 2 young brothers reported that the disease became evident at the same time, almost to the day, sixteen months prior to examination by a physician. The results of sigmoidoscopic and roentgen examination of the 2 patients were almost identical. In a second family 3 young members were involved by a severe process which ended fatally.

The close relation between certain aspects of ulcerative colitis and psychologic disturbances is fairly generally recognized. Daniels<sup>269</sup> in a careful psychiatric study of 25 persons suffering from the disease comes to what is usually the accepted conclusion—that except for the basic factors relating emotions to disturbances of the large intestine, the psychophysiologic mechanism of ulcerative colitis is not understood. He does make one important observation, which should be clear to all physicians familiar with the variations in the disease, namely, that recurrences may bear a significant relation to emotional disorders and at times the symptoms mask a severe depression. He also points out the fact still too infrequently considered that in many instances there is a direct relation between the severity of the physical reaction of the disease and the underlying psychopathologic condition.

The relation between ulcerative colitis and allergic disturbances is also fairly well recognized. Many observers are convinced that it is not a primary allergic phenomenon but that allergic manifestations are important complications of the condition. Andresen,<sup>270</sup> however, is convinced that in a large proportion of patients suffering from ulcerative colitis the disease develops solely on the basis of abnormal sensitivity to food allergens. He regards the resemblance between the mucosal lesions of ulcerative colitis and allergic reactions of the skin as quite obvious. The results obtained by Andresen in a series of 50 cases cannot be ignored and undoubtedly reflect the excellent care which the patients received. The article, however, is not convincing as a demonstration of the origin of the condition. Nevertheless, the details involved in the treatment outlined by this author should be read with care and should form the basis of helpful therapy in many instances.

The complications encountered in the course of ulcerative colitis are known and have been frequently described by Bargen and others, but the number of patients with this disease encountered by the average physician in practice is relatively small. For this reason it is quite proper

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269. Daniels, G. E.: *Psychiatric Aspects of Ulcerative Colitis*, New England J. Med. **226**:178, 1942.

270. Andresen, A. F. R.: *Ulcerative Colitis—An Allergic Phenomenon*, Am. J. Digest. Dis. **9**:91, 1942.

in a review of this sort to mention periodically some of the less usual manifestations of the condition. One of the not too uncommon complications is associated arthritis, which can usually be properly classified as rheumatoid in nature. As has been pointed out by other authors, the activity of the arthritic process is apt to coincide with exacerbations of the colitis, and favorable results following colectomy, as far as the course of the arthritis is concerned, are usually to be expected. Presumably, in such instances the colon actually behaves as a focus of infection. One such instance is adequately described by Wright.<sup>271</sup> Bargaen's contribution to knowledge of the clinical manifestations of the disease has been outstanding. In a recent note,<sup>272</sup> he calls attention to a most unusual complication, namely, nephrolithiasis. In all 6 cases reported by the author renal stones apparently developed some years after a permanent ileostomy had been performed. In 4 instances the renal calculi were bilateral, and in each instance infection of the urinary tract was present. It is of incidental interest that in 3 cases the patients suffered from frequent attacks of arthritis. The mechanism underlying the formation of such calculi is not clear and might well form the basis of careful studies on the metabolism of calcium and phosphorus in ileostomized subjects. A further report by Hopping and Bargaen<sup>273</sup> describes the condition as a disease of complications, and in addition to mentioning personal difficulties, also notes the exhibition of other conditions, such as arthritis, cardiac disease, iritis, erythema nodosum and nephritis. Another not infrequent clinical manifestation associated with chronic ulcerating disease of the colon is that of cutaneous changes. Felsen<sup>274</sup> reports 3 instances of a rather unusual type of cutaneous manifestation complicating this disease. In each case during an exacerbation of the colitis multiple areas of cutaneous necrosis, generally discrete but sometimes confluent, appeared. The lesions started as small, painful, reddened papules, in which subsequently developed a central zone of necrosis and ulceration. In all of the lesions the floor of the ulcer was formed by muscle or fascia. Besides the rapidly necrotizing character of the lesions, two striking features were the depth and the extension of the subcutaneous involvement. Cultures of material from the lesions revealed the presence of *E. coli*, *Staphylococcus aureus* and nonhemolytic strepto-

271. Wright, A. D.: Ulcerative Colitis Complicated by Polyarthritides Treated by Total Colectomy, *Proc. Roy. Soc. Med.* **25**:189, 1942.

272. Bargaen, J. A.: Nephrolithiasis Complicating Ulcerative Colitis After Ileostomy: A Report of Six Cases, *J. Urol.* **46**:183, 1941.

273. Hopping, R. A., and Bargaen, J. A.: Cases of Chronic Ulcerative Colitis Encountered at the Clinic in 1939, *Proc. Staff Meet., Mayo Clin.* **17**:151, 1942.

274. Felsen, J.: Multiple Necrotizing Skin Lesions in Chronic Ulcerative Colitis, *New York State J. Med.* **41**:2228, 1941.

cocci; no anaerobic organisms were found. Elsom and his colleagues<sup>275</sup> call attention to a phenomenon already pointed out by Mackie that is of particular interest in cases of complicated ulcerative colitis. In 7 ileostomized patients nitrogen balance studies were carried out, and it was shown that the nitrogen excretion in the ileal discharge was abnormally great in 4 of them. This finding is entirely in keeping with the frequent demonstration of transient changes in the terminal portion of the ileum suggesting an actual disease process. As these authors point out, however, roentgen and clinical evidence of ileal involvement practically always disappears coincident with clinical improvement of the underlying colitis, and it is highly probable that it is a nutritional disturbance, rather than any actual inflammatory disease of the small intestine.

The etiologic role of "*Bacterium necrophorum*" in ulcerative colitis has been studied for some time by Dragstedt and his collaborators.<sup>276</sup> A summary of the work, with a discussion of the complicating factors, is of interest but leaves one with a good deal of doubt as to the final significance of the results. Similarly, a clinical study by Henderson, Pinkerton and Moore<sup>277</sup> concerning "*Histoplasma capsulatum*" as a cause of the disease is to be mentioned.

Therapeutic measures that apparently have been efficacious in the hands of different investigators are numerous. Whether one agrees with the specificity of the measures employed, it is of interest to mention them in the hope that subsequent experience will make it possible to evaluate their importance. Winkelstein and Shwartzman<sup>278</sup> claim that they obtained marked improvement in 20 of 29 patients with nonspecific ulcerative colitis after the use of a concentrated and purified antitoxic *E. coli* serum. Weiss, Slanger and Goodfriend<sup>279</sup> believe that they have observed excellent results following the use of mixed vaccines prepared from cultures of material taken from the nose, throat and rectosigmoid

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275. Elsom, K. A.; Dickey, F. G., and Chornock, F. W.: Functional Disturbances of the Small Intestine in Chronic Idiopathic Ulcerative Colitis, *Am. J. Digest. Dis.* 9:74, 1942.

276. Dragstedt, L. R.; Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis: A Summary of Evidence Implicating *Bacterium Necrophorum* as an Etiologic Agent, *Ann. Surg.* 114:653, 1941.

277. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: *Histoplasma Capsulatum* as a Cause of Chronic Ulcerative Enteritis, *J. A. M. A.* 118:885 (March 14) 1942.

278. Winkelstein, A., and Shwartzman, G.: The Use of Concentrated and Purified Antitoxic *B. Coli* Serum in the Treatment of Indeterminate Ulcerative Colitis, *Am. J. Digest. Dis.* 9:133, 1942.

279. Weiss, S.; Slanger, A., and Goodfriend, S.: The Relation of the Nasopharynx to Ulcerative Colitis, *J. Lab. & Clin. Med.* 27:1925, 1941.



mucosa. Obviously, no specificity can be claimed for such a measure. Streicher<sup>280</sup> has observed the results following the use of azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3', 6'-disulfonate) and sulfathiazole and has come to the conclusion that little or no improvement is obtained by the use of these preparations, except in cases of mild disease. He is of the opinion that medical treatment for the most part is indicated in this disease and limits the use of ileostomy, with or without colectomy, to those patients in whom the colon has undergone irreparable change. Recent reports on sulfonamide therapy have to do principally with the use of sulfaguanidine. Kirsner and his associates<sup>281</sup> conclude that the use of this drug in chronic, nonspecific ulcerative colitis has not yet yielded any striking therapeutic results. Variable results were obtained by Stickney, Heilman, Bargaen and Dearing<sup>282</sup> on a group of 46 patients. They also feel that it is impossible to state with any degree of certainty that the drug is responsible for the favorable response obtained in some of their patients. Many failures were observed, and they feel that the exact place of sulfaguanidine in the progress of the therapy of ulcerating intestinal disease has not been established. In view of previous favorable reports the article by Shiffer and Ferguson<sup>283</sup> regarding the use of a concentrated liver extract and vitamin B<sub>1</sub> is of interest. These authors consider that these medications have contributed nothing to the treatment of this disease, except possibly from the point of view of replacement.

Parenthetically, it will not be amiss to stress again the striking manifestations of deficiency disease so frequently noted as a secondary manifestation of prolonged diarrhea. Frequent attention has been called to this circumstance, and the necessity for replacement therapy cannot be too strongly emphasized. Additional articles mentioning such manifestations have been presented recently by Molina,<sup>284</sup> Diaz y Rivera,<sup>285</sup>

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280. Streicher, M. H.: Chronic Ulcerative Colitis: A Clinical Summary of the Management in Nine Hundred and Twelve Cases, *J. A. M. A.* **118**:431 (Feb. 7) 1942.

281. Kirsner, J. B.; Rodaniche, E. C., and Palmer, W. L.: Use of Sulfaguanidine in Nonspecific Ulcerative Colitis and Other Infections of the Bowel, *Proc. Inst. Med. Chicago* **14**:53, 1942.

282. Stickney, J. M.; Heilman, F. R.; Bargaen, J. A., and Dearing, W. H.: Sulfaguanidine in Ulcerative Intestinal Disease, *Proc. Staff Meet., Mayo Clin.* **17**:33, 1942.

283. Shiffer, P., and Ferguson, L. K.: The Treatment of Idiopathic Ulcerative Colitis with Concentrated Liver Extract and Vitamin B<sub>1</sub>, *Am. J. Digest. Dis.* **8**:300, 1941.

284. Molina, R. R.: Sprue in Puerto Rico: A Clinical Study of One Hundred Cases, *Puerto Rico J. Pub. Health & Trop. Med.* **17**:134, 1941.

285. Diaz y Rivera, R. S.: The Prothrombin Time in Tropical Sprue, *Puerto Rico J. Pub. Health & Trop. Med.* **17**:124, 1941.

Oettel and Thaddea<sup>286</sup> and Bercovitz.<sup>287</sup> These articles deal with manifestations of avitaminosis A and B<sub>1</sub>, prolongation of prothrombin time, hypoproteinemia and avitaminosis C, respectively.

Appraisal of medical versus surgical therapeutic measures is still difficult. The complications following ileostomy and colectomy, as previously indicated, should not be ignored. There can be little doubt that there is a real place for radical surgical intervention in this condition, but as a rule its undertaking is unwise unless adequate medical measures have failed to control the situation. In many instances medical measures suffice to maintain a patient in relatively good health, but it seems proper to point out that maintenance of life alone by medical means is not a justification for the continuation of medical treatment. Once a patient with ulcerative colitis fails to maintain himself as a useful, ambulatory individual, it is important to recognize that medical therapy has failed and that an indication exists for proper surgical intervention. Perusal of the articles by Reed and Rochex,<sup>288</sup> Elsom and Ferguson<sup>289</sup> and Cave and Thompson<sup>290</sup> should prove worth while, as they all contain interesting discussions of this moot question.

*Cancer of the Colon and the Rectum.*—Examples of malignant lesions occurring in early life continue to multiply. Kennedy,<sup>291</sup> Oosting,<sup>292</sup> Laird<sup>293</sup> and Pennell and Martin<sup>294</sup> report the occurrence of such malignant manifestations in infants and children. The report of Kennedy is particularly pertinent inasmuch as he records 49 cases of rectal and colonic polyps in infants and children. The patients ranged in age from 6 months to 13 years, and the lesions were visualized by proctoscopic or

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286. Oettel, H., and Thaddea, S.: Hypoproteinemia in Nontropical Sprue, *Deutsches Arch. f. klin. Med.* **187**:353, 1941.

287. Bercovitz, Z.: Recent Advances in the Treatment of Chronic Ulcerative Colitis, *M. Clin. North America* **24**:683, 1940.

288. Reed, A. C., and Rochex, F.: Treatment of Chronic Ulcerative Colitis Based on Thirty Cases, *Northwest Med.* **40**:332, 1941.

289. Elsom, K. A., and Ferguson, L. K.: Appraisal of Medical Versus Surgical Treatment of Idiopathic Ulcerative Colitis: Follow-Up Data on Fifty Cases, *Am. J. M. Sc.* **202**:59, 1941.

290. Cave, H. W., and Thompson, J. E.: Mortality Factors in the Surgical Treatment of Ulcerative Colitis, *Ann. Surg.* **114**:46, 1941.

291. Kennedy, R. L. J.: Polyps of the Rectum and Colon in Infants and in Children, *Am. J. Dis. Child.* **62**:481 (Sept.) 1941.

292. Oosting, M.: Adenocarcinoma of the Sigmoid Colon, Rectum, and Anus in Children: Report of Two Cases in a Thirteen-Year Old Girl and an Eight-Year-Old Boy with Summary of Recorded Cases up to Fifteen Years of Age, *Ohio State M. J.* **37**:1067, 1941.

293. Laird, T. K.: Carcinoma of the Colon in a Child of Fourteen Years with a Review of the Literature, *Am. J. Surg.* **53**:335, 1941.

294. Pennell, V., and Martin, L. C.: Carcinoma of the Colon in Children with Report of a Case, *Brit. J. Surg.* **29**:228, 1941.

roentgen examination. The hereditary character of polypoid disease of the colon is mentioned, as well as the tendency to malignant degeneration.

A critical commentary on the tardiness with which rectal cancer is diagnosed is made by Braund and Binkley<sup>295</sup> on the basis of 108 unselected patients. The facts presented are not new but deserve comment. Symptoms had been present for an average period of eight to ten months before the patients sought medical advice. Of 100 patients the disease was diagnosed without undue delay in only 25 after they were referred to a physician. For the remaining 75 there was an additional average delay of between nine and ten months, during which time they received inadequate and improper therapy. Twenty patients had not had a rectal examination, although more than 90 per cent of rectal cancers were within reach of the examining finger. Thirty-seven had been examined digitally but improperly, with the result that no mass was detected before the patients were referred to the clinic. Forty-six of the 100 patients saw between two and five physicians before being referred for a final diagnosis. In the face of such facts, which unfortunately are not unusual, it is small wonder that the early diagnosis of cancer still leaves much to be desired.

Unlike cancer of the stomach, recognition of metastases in the presence of cancer of the colon and the rectum seems to be readily accomplished by the exploring surgeon, as shown in a study by Mayo and Schlicke.<sup>296</sup> In those cases in which death occurred shortly after resection, no metastases were encountered at necropsy in more than four fifths of those cases in which none was found at operation. Residual cancer was encountered in only 5 per cent of the cases in which death occurred shortly after resection. An important comment is made by these authors when they state that in their opinion independent growths are frequently responsible for many "recurrences." For this reason, they suggest that whenever a carcinoma is encountered in any portion of the colon or the rectum, the presence of a second carcinoma must be carefully ruled out. A study by Collier, Kay and MacIntyre<sup>297</sup> similar to the one already reviewed<sup>154</sup> on regional lymphatic metastases of carcinoma of the stomach by the same authors is presented in relation to the colon. Here again, a large number of specimens of cancer of the colon were carefully studied, with a minute examination of the regional

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295. Braund, R. R., and Binkley, G. E.: Plea for Earlier Diagnosis of Rectal Cancer: Analysis of One Hundred and Eight Clinic Patients, *New York State J. Med.* **42**:33, 1942.

296. Mayo, C. W., and Schlicke, C. P.: Carcinoma of the Colon and Rectum: A Study of Metastasis and Recurrences, *Surg., Gynec. & Obst.* **74**:83, 1942.

297. Collier, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Colon, *Ann. Surg.* **114**:56, 1941.

lymph nodes. An average of 52 nodes were isolated in each specimen and were examined for metastatic involvement. Two thirds of the specimens showed such involvement. There was no essential difference in the spread noted in carcinoma of the right half and of the left half of the colon. As a careful anatomic study this report should be read by all surgeons. An unusual association of rectal cancer is mentioned by Nordlander,<sup>298</sup> who reports a group of cases in which primary cancer was encountered simultaneously in the uterus and in the rectum.

Because of the frequent occurrence of cancer of the rectum an article by Bowling and Dixon<sup>299</sup> on advances in the treatment of this disease is significant and encouraging. One important comment on therapy lies in the statement that electrosurgery, or actual cauterization, radium therapy and roentgen therapy are not competitive measures but are decidedly complementary in nature. Reason for the hope that early diagnosis of carcinomatous lesions of the colon and the rectum will be associated with successful therapy is illustrated in the statistics presented by Bergen and his collaborators.<sup>300</sup> Of 61 patients on whom operations were performed for carcinomatous lesions less than 2.5 cm. in diameter (in other words, early lesions), 28 were living at the end of five years and 24 at the end of seven years. It is of incidental interest to note that in 47 of the 61 patients the lesions were located within easy reach of the examining finger or of a sigmoidoscope, an indication of the necessity for early examination.

Previous mention has been made of carcinoid tumors, most of which occur in the appendix. Waugh and Snyder<sup>301</sup> mention that only 11 carcinoid tumors of the colon have been reported, in 5 of which the lesion was in the cecum. The authors report 1 additional case, in which the cecum was involved.

Although admitting that it is generally held that radical surgical intervention is the measure of choice in the treatment of multiple polyposis of the colon, Vanzant<sup>302</sup> recommends the employment of roentgen therapy. He reports 2 cases in which the condition appeared to respond favorably to irradiation. Whether such a measure is justifiable remains

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298. Nordlander, E.: Primary Cancer in the Uterus and in the Rectum of the Same Patient, *Acta radiol.* **22**:439, 1941.

299. Bowling, H. H., and Dixon, C. F.: Advances in the Treatment of Carcinoma of the Rectum, *M. Clin. North America* **25**:915, 1941.

300. Bergen, J. A.; Cromar, C. D. L., and Dixon, C. F.: Early Carcinoma of the Colon: I. Nature and Adequate Treatment of the Small Carcinoma, *Arch. Surg.* **43**:186 (Aug.) 1941.

301. Waugh, J. M., and Snyder, J. M.: Carcinoid Tumor of the Cecum, *Ann. Surg.* **114**:151, 1941.

302. Vanzant, B. T.: Roentgen Therapy in Hereditary Diffuse Polyposis of the Colon, *J. A. M. A.* **118**:875 (March 14) 1942.

open to some question, but there can be little doubt that irradiation therapy of cancer of the rectum is at times justified. Such treatment probably should be used only as a palliative measure, however, and the results of irradiation are carefully presented by Sharp.<sup>303</sup> In addition, he records apparently favorable results, with eradication of the growth by irradiation, in 13 patients who were followed up for four to eight years. This group received high voltage roentgen therapy to skin tolerance combined with implantation of seeds.

Cases of malignant growth of the anus are not too frequent. For this reason the report by Lawrence<sup>304</sup> of 2 instances of basal cell epithelioma of the anus are worthy of comment. Apparently, only 4 cases have been previously reported.

*Appendicitis.*—The causes leading to acute appendicitis are still not entirely understood. For this reason the study by Dennis<sup>305</sup> on the physiologic behavior of the appendix in human beings and the problem of appendicitis is of more than academic interest. This author attempted experiments on 272 excised appendixes in order to determine the contractility and the resistance to flow through the lumen of the organ. Evidence is presented that acute, suppurative appendicitis, but not gangrene, may be initiated by spasm of the portion of the muscle wall of the appendix, although the stimulus for this spasm is not known. The author found that inflamed appendixes presented an average resistance to outflow of fluid through the appendix into the cecum which was twice that observed in normal specimens. Figures obtained on "interval" specimens fell between these two values. Appendical pain, Dennis believes, including the pain radiating to the right lower quadrant of the abdomen, is largely due to tension on the muscular wall of the organ and may be ameliorated by epinephrine. He states that seepage of infected fluid through the appendical wall occurs at levels of intraluminal tension commonly reached in appendicitis, and he offers this as an explanation of many cases of peritonitis without rupture. Rupture of the organ during an acute attack he believes to be due to digestion of the wall, inasmuch as the normal appendical wall can withstand an intraluminal tension of 2 atmospheres. Completely obstructed appendixes, he believes, may remain uninflamed because of loss of the secretory power of the mucosa.

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303. Sharp, G. S.: The Radiation Treatment of Cancer of the Rectum: Technique for Radium Needles Through Perineal Stab Wounds, *Am. J. Roentgenol.* **46**:207, 1941.

304. Lawrence, K. B.: Basal Cell Epithelioma of the Anus: Report of Two Cases, *Arch. Surg.* **43**:88 (July) 1941.

305. Dennis, C.: Physiologic Behavior of the Human Appendix and the Problem of Appendicitis, *Arch. Surg.* **43**:1021 (Dec.) 1941.

The relation between oxyuriasis and appendicitis continues to attract attention, and reports by Schwarz and Straub,<sup>306</sup> Morehead<sup>307</sup> and Ashburn<sup>308</sup> attest to the frequency with which this association is encountered. Of extreme importance is the report of Straus<sup>309</sup> on 2 cases in which infectious mononucleosis simulated acute appendicitis. It is not generally recognized that this infectious disease may at times be associated with fulminating attacks of abdominal pain. That such may be the case is illustrated by Straus's report. In 1 case atypical hyperplasia of the lymphoid tissue of the appendix was described, which was identical with the lesions encountered in the lymph glands of patients with infectious mononucleosis. Inasmuch as this disease is characterized by typical changes in the blood smear, it is important to emphasize the necessity of careful examinations of the blood in cases of acute conditions in the abdomen before resorting to surgical procedures.

The frequency of occurrence of acute appendicitis is illustrated in a statistical report by Petré,<sup>310</sup> who describes the incidence of this condition in southwestern Sweden and refers to a similar statistical study by Quensel. According to these authors, it would appear that if one takes the life span as a whole, 12.5 per cent of the total population could be expected to have acute appendicitis. The mortality from appendicitis still remains reasonably high due to lack of public education and too long a delay between the onset of symptoms and proper operative procedures. The improper use of laxatives undoubtedly continues to be a contributing cause. An unusual comment is made by Jennings and his associates,<sup>311</sup> who suggest that the factor of fatigue on the part of the operating room team, the surgeon and the patient may be of importance in bringing about the death of the patient. They suggest that after admission to the hospital and diagnosis, night operations be avoided in the absence of signs of spreading peritonitis, in order to overcome the aforementioned factor and to adjust the frequently disturbed electrolyte balance of the patient. These authors, in conjunction with many others, strongly recommend

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306. Schwarz, J., and Straub, M.: Oxyuriasis and Appendicitis, *Arch. Path.* **33**:28 (Jan.) 1942.

307. Morehead, R. P.: The Pinworm and the Appendix, *North Carolina M. J.* **2**:349, 1941.

308. Ashburn, L. L.: Appendiceal Oxyuriasis: Its Incidence and Relationship to Appendicitis, *Am. J. Path.* **17**:841, 1941.

309. Straus, R.: Infectious Mononucleosis Simulating Acute Appendicitis with Description of a Specific Lesion of the Appendix, *Am. J. Clin. Path.* **12**:295, 1942.

310. Petré, G.: Question of Frequency of Acute Appendicitis, *Chirurg* **13**:236, 1941.

311. Jennings, J. E.; Burger, H. H., and Jacobi, M.: Acute Appendicitis: A Clinical and Pathologic Study of 1,680 Consecutive Cases, *Arch. Surg.* **44**:896 (May) 1942.

the wider use of the McBurney incision. The use of sulfanilamide powder in the wound has cut down minor complications in the absence of drainage and has permitted a tighter closure of the incision when drainage has been used. Its intraperitoneal use may be beneficial in early peritonitis, according to Deaver.<sup>312</sup> Taylor and Hodges<sup>313</sup> believe that it contributes little once peritonitis has developed. In a frank discussion of the causes of death from acute appendicitis Aud<sup>314</sup> courageously states that some lives might have been saved by more careful preoperative examination and preparation, a better selection of time for operation, a different type of operation and more intensive and better postoperative treatment. He deplors the frequent lack of adequate operative notes and postoperative records and is properly impressed by the fact that in 90 per cent of deaths in a certain area, no autopsies had been done to determine the exact cause of death. A plea for more general education of the public as a means of preventing deaths from this condition is made by Cutler and Hoerr,<sup>315</sup> who state that in their series the mortality rate from acute appendicitis remains the same as it did twenty-five years ago, in spite of advance in surgical technic. Hill and Fellman<sup>316</sup> also insist on the fatal consequences of delay in diagnosis. In over one fifth of the fatal cases in their series of over 1,000 the patients received purgatives, although the authors believe that this does not necessarily mean that the purgatives caused the deaths. They suggest the probability that the important factor was the delay occasioned by the patients staying at home and receiving family care with familiar household remedies for some time before consulting a physician. Education of the community and of the medical profession appears to have produced favorable results according to the report given by Carraway.<sup>317</sup> This author believes that the reduction in the mortality in his series is due in part to the following factors: a correct taking of history and careful physical examination, permitting an early diagnosis; insistence that the family physician does not procrastinate and that if in doubt he procure a competent consultant, and assignment of patients with peritonitis to only the most thoroughly trained and experienced surgeons.

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312. Deaver, J. M.: *Acute Appendicitis in Children*, Pennsylvania M. J. **45**: 358, 1942.

313. Taylor, E. S., and Hodges, R. G.: *Acute Appendicitis in Children*, Surg., Gynec. & Obst. **73**:288, 1941.

314. Aud, G.: *Deaths from Acute Appendicitis in Louisville*, South. M. J. **34**:914, 1941.

315. Cutler, E. C., and Hoerr, S. O.: *Acute Appendicitis: Twenty-Five-Year Study*, J. Michigan M. Soc. **41**:203, 1942.

316. Hill, G. C., and Fellman, A. C.: *Acute Appendicitis: A Study of 1006 Consecutive Cases*, Nebraska M. J. **26**:359, 1941.

317. Carraway, C. N.: *Management of Patients with Appendicitis with Special Reference to Those with Perforation*, J. Alabama M. A. **11**:91, 1941.

An excellent statistical study of 671 cases of appendical peritonitis is given by Rogers and Faxon.<sup>318</sup> In the absence of a palpable mass the authors urge the use of a clinical basis for the appraisal of each individual case and feel that the success of treatment will be determined by ability to recognize in advance those cases in which localization of peritoneal infection will or will not take place and ability to select the safest time for operation, together with good preoperative and postoperative care. The greatest mortality was noted in those patients who looked ill on admission and were operated on more than six hours after an incident interpreted as acute perforation. This appearance of being very ill they believe to be the most unfavorable prognostic sign; absence of active peristalsis they believe is next in importance, and a pulse rate too rapid for the white cell count is the most unfavorable laboratory finding. From a study of 227 cases in which a mass was palpable they conclude that operation should rarely be done under such circumstances on the fifth, the sixth or the seventh day of illness and that incision and drainage alone should be carried out. Appendectomy should be performed within six weeks of this procedure. They are firmly convinced that even when a localized lesion has formed, the general clinical impression that the patient presents at entry, of being very ill or not very ill, is of more reliable prognostic significance than any laboratory data.

An interesting laboratory observation is reported by Lesser and Kaufman.<sup>319</sup> In 99 cases of acute appendicitis in which the diagnosis was confirmed by operation, blood sedimentation rates were normal. In 33 additional cases in which patients with conditions given a preoperative diagnosis of acute appendicitis were operated on, elevated sedimentation rates were obtained. In 18 of these cases complicating appendical abscesses or general peritonitis of varying degree was presented; in 15 cases, the diagnosis of appendicitis was erroneous and extra-appendical conditions were encountered. The authors would seem to be justified in concluding that in an abdominal condition simulating acute appendicitis, the finding of an abnormally high sedimentation rate should indicate either a serious complication or extra-appendical disease.

The question of chronic appendicitis is a hardy perennial. Warren and Ballantine<sup>320</sup> record the results of appendectomy for recurrent pain

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318. Rogers, H., and Faxon, H. H.: A Statistical Study of Six Hundred and Seventy-One Cases of Appendiceal Peritonitis: I, *New England J. Med.* **226**: 707, 1942. Faxon, H. H., and Rogers, H.: A Statistical Study of Six Hundred and Seventy-One Cases of Appendiceal Peritonitis: II, *ibid.* **226**:745, 1942.

319. Lesser, A., and Kaufman, L. R.: Five Year Survey of Blood Sedimentation Test in Acute Appendicitis, *Surg., Gynec. & Obst.* **73**:163, 1941.

320. Warren, R., and Ballantine, H. T., Jr.: Chronic Appendicitis: Results After Appendectomy for Recurrent Pain in Right Lower Quadrant of the Abdomen, *J. A. M. A.* **117**:994 (Sept. 20) 1941.



in the right lower quadrant of the abdomen. Of a series of 138 cases in which an inflamed appendix was removed, the operative specimen in 49 showed typical "chronic appendicitis" on histologic examination. Of the entire group, in about three fourths partial or complete relief of preoperative symptoms was experienced, but the authors take pains to point out that in those cases in which there were long histories or numerous attacks the percentage of good end results was not so high as in those in which there were short histories or few attacks. They admit that the mortality from the operation is low but rightfully state that the morbidity and the period of incapacity following operation cannot be ignored. For this reason they urge the adoption of a more conservative attitude toward operative procedures for chronic appendicitis.

Clarke and Shapiro<sup>321</sup> comment on 3 cases of acute appendicitis in which pain was not the first symptom. Such a clinical observation is of real importance. In 1 instance a shaking chill preceded the onset of pain by several hours; in a second, malaise and vomiting were the initial symptoms and lasted for some time, and in a third case, the appearance of pain was preceded by seventeen hours of malaise, fainting and vomiting. The necessity of an accurate physical diagnosis in the presence of such atypical pictures is obvious.

From the foregoing comments and reports, it would seem imperative that members of the medical profession in this country take the matter of appendicitis even more seriously than at present and increase their efforts to educate not only the public but other members of their profession as to the proper moves to be made in the treatment of this dangerous condition.

*Miscellaneous Observations.*—An unusual type of observation is that reported by Paine and Nessa<sup>322</sup> on the distribution and transport of gas in the gastrointestinal tract of infants and young children. Roentgenograms of the abdomen were made on 46 children, varying in age from a few minutes to 10 years. All of these infants and children were thought to have normally functioning digestive tracts. It was found that up to 18 months of age gas was distributed equally between the small bowel and the colon, between 18 months and 6 years of age more and more intestinal gas was located in the colon and less in the small bowel and after 7 years of age, as in adulthood, no gas was normally present in the small bowel. Serial roentgenograms of the abdomen were made on 7 newborn infants. In each case gas was observed to be already

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321. Clarke, R., and Shapiro, M.: Pain in Acute Appendicitis, *Lancet* 2:39, 1941.

322. Paine, J. R., and Nessa, C. B.: Observations on the Distribution and Transport of Gas in the Gastrointestinal Tract of Infants and Young Children, *Surgery* 11:281, 1942.

present in the stomach, duodenum or jejunum by the time the first roentgenogram could be taken, as soon as possible after birth, which was within six to fifteen minutes and within four to six hours after birth gas was present in the sigmoid flexure of the colon or the rectum.

An unusual form of injury to the gastrointestinal tract is discussed by Poer and Woliver.<sup>323</sup> They comment on the problem of subparietal intestinal injury due to nonpenetrating abdominal trauma. A study of a large series of cases revealed the interesting fact that a relatively high percentage of injuries was due to a relatively small variety of accidents, which included injuries due to personal encounters, in which the patient was struck or kicked in the abdomen or fell on it; the results of industrial accidents caused by blunt objects, and accidents concerned with transportation, frequently with motion at a high rate of speed. Distention of the intestine with fluid or with food contributed to the likelihood of rupture, as was evidenced by the fact that many injuries were received soon after the patients had eaten. The necessity for early intervention is stressed. Duodenal rupture with fat necrosis but without evident pancreatic injury is a rare abdominal condition following trauma. Two cases of such a condition are reported by Dixon.<sup>324</sup>

A more general recognition of the dangers inherent in heavy radiation to the intestinal tract or to neighboring structures is apparent from recent articles. Warren and Friedman<sup>325</sup> provide an excellent discussion of the pathology and pathologic diagnosis of radiation lesions in the gastrointestinal tract, which should be of interest not only to the pathologist but to the internist. This is particularly true since a determination on pathologic grounds as to whether a given lesion is entirely or in part due to irradiation may have importance for further therapy. Thirty-eight cases were selected for study, including ulcers, fistulas and strictures which developed at sites distant from neoplastic tissue subjected to irradiation or at the site of a partially or completely destroyed tumor. The bowel wall was usually thickened and indurated, with an opaque serosa, and telangiectasia was prominent. Similar involvement was frequently noted in the adjacent mesentery. The mucosa of the bowel rarely appeared entirely normal, but usually, even in the non-ulcerated lesions, atrophy and fixation to the submucosa were seen. The degree of ulceration ranged from confluent, superficial erosions to deep, punched-out ulcers. Stenosis was sometimes due to diffuse sclerosis

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323. Poer, D. H., and Woliver, E.: Intestinal and Mesenteric Injury Due to Non-Penetrating Abdominal Trauma, *J. A. M. A.* **118**:11 (Jan. 3) 1942.

324. Dixon, G. G.: Duodenal Rupture and Fat Necrosis: Report of Two Cases, *Ann. Surg.* **114**:147, 1941.

325. Warren, S., and Friedman, N. B.: Pathology and Pathologic Diagnosis of Radiation Lesions in the Gastro-Intestinal Tract, *Am. J. Path.* **18**:499, 1942.

with general constriction of a segment and sometimes to formation of a stricture at a site of ulceration. Necrosis was part of most reactions, and in extreme instances the reaction approached massive gangrene. The necessity of a knowledge of the existence of such lesions should be obvious to those interested in irradiation therapy. Experimental observations were made by the same authors<sup>326</sup> on the evolution of radiation ulcers of the intestine. The observations were made on rabbits, which received a course of irradiation totaling 4,000 r distributed in eight to ten doses given approximately every other day. Lesions of the bowel developed slowly, and ulcerations became more marked during the second and the third month after therapy. The histologic findings are of interest but do not warrant detailed discussion. These two articles, with reference to previous work, such as that done by Engelstad (1938) and Ferguson (1938), represent a real contribution. A somewhat related series of observations is to be found in an article by K'o, Tu and Chan.<sup>327</sup> These authors were interested in the possibly unfavorable effects that might occur during the administration of iron while patients were undergoing irradiation therapy. Experiments were made on dogs, and it was found that ferrous sulfate was definitely valuable in the treatment of anemia as a result of chronic blood loss and caused no harmful effects while the animals were undergoing abdominal irradiation. When ferrous citrate was given in therapeutic doses under similar circumstances, gross intestinal lesions occurred. The lesions noted appeared to be similar to those described by Warren and Friedman.

Megacolon has received a certain amount of attention during the past year. Etzel<sup>328</sup> goes so far as to raise the question whether the disease complex that includes megaesophagus, megacolon and megaureter, may be caused by chronic vitamin B<sub>1</sub> deficiency. The paper is based on a study of 170 cases, with pathologic studies on 16 autopsy specimens, encountered in the region of São Paulo, Brazil. Degeneration in the intramural autonomic nervous system is believed to be the anatomic basis for these manifestations, and the author has attempted to link this with the evidence of a vitamin B<sub>1</sub> deficiency believed to be due to the dietary habits of the local population. The article is far from convincing, but the subject matter presented offers the basis for interesting speculations. A different concept of the possible relation between disorders of

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326. Friedman, N. B., and Warren, S.: Evolution of Experimental Radiation Ulcers of the Intestine, *Arch. Path.* **33**:326 (March) 1942.

327. K'o, Y. K.; Tu, C. L., and Chan, B. C.: The Effect of Hard Roentgen Rays on Intestines of Normal Dogs Fed on Inorganic Iron Compounds, *Surg., Gynec. & Obst.* **73**:333, 1941.

328. Etzel, E.: May the Disease Complex That Includes Mega-Esophagus (Cardiospasm), Megacolon and Mega-Ureter Be Caused by Chronic Vitamin B<sub>1</sub> Deficiency? *Am. J. M. Sc.* **203**:87, 1942.

the nervous system and megacolon is presented by Vidal,<sup>329</sup> who believes that hypothalamic disturbances may be of some etiologic importance in this condition. This investigator destroyed in rats the medial preoptic area and the lateral hypothalamus and adjacent areas by means of a unipolar electrode and observed after several weeks the development of megacolon. In a discussion of the therapeutic measures applicable to congenital megacolon, Soper<sup>330</sup> considers that sympathectomy should be discarded. He bases such an opinion on a review of the literature and his own personal observations, particularly in 1 case, in which presacral sympathectomy was followed by a marked reduction in the size of the colon but at the same time permitted a volvulus to occur from the markedly lengthened mesentery of the small bowel. Prior to the development of this acute condition in the abdomen uncontrollable diarrhea had been present as an aftermath of the operative procedure. He believes that resection of the colon, according to Dixon's method, should be employed in all cases, with the possible exception of those in which the patient is suffering from a severe form of malnutrition. In these cases he advocates the performance of an ileostomy, with subsequent colectomy as an elective procedure. He records the experiences of 12 patients who have been treated by such a radical procedure.

Kantor,<sup>331</sup> as usual, contributes an observation of interest in the description of what he terms the "diaphragmatic flexure." By this term he describes a splenic flexure which is located directly under the left side of the diaphragm and which he was able to demonstrate in about 15 per cent of almost 1,000 patients studied. It is often associated with a redundant colon. This anatomic anomaly is associated with symptoms only when other conditions exist, such as the presence of gas due to colonic malfunction. When symptoms do occur in connection with this condition, Kantor points out that the most important ones are those associated with the production of heartburn, thoracic distress and cardiac embarrassment. The colonic origin of heartburn has heretofore been overlooked and is accordingly emphasized. Kantor states that the thoracic symptoms occur whether or not organic heart disease is present. Appropriate therapeutic measures obviously must include those calculated to bring about effective colonic evacuation. The importance of the article lies in the fact that here is another possible source of confusion in the interpretation of symptoms relating to the possible existence of heart

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329. Vidal, F.: Hypothalamus and Megacolon, *Arch. argent. de enferm. d. ap. digest. y de la nutrición* 17:310, 1941-1942.

330. Soper, H. W.: Megacolon, *Am. J. Roentgenol.* 46:655, 1941.

331. Kantor, J. L.: Colon Studies: VIII. The Diaphragmatic Flexure, *Am. J. Roentgenol.* 4:417, 1942.

disease. I am in entire accord with the suggestions made by the author, and my attention has been called to such a possible source of "cardiac symptoms" by Dr. T. R. Harrison. The exact mechanism underlying the production of such symptoms, however, is not at all clear and should be studied.

An unusual occurrence is that noted by Lemman and Paschal,<sup>332</sup> who report a case of rupture of the stomach following the ingestion of sodium bicarbonate. They record 31 cases of spontaneous rupture of the stomach reported in the literature. In this particular instance, the accident followed the ingestion of a large amount of food and alcohol, following which the patient took bicarbonate of soda in generous doses for relief of abdominal fullness.

An unusual source of food poisoning is reported by Frant and Irving<sup>333</sup> and may be of some importance. These authors report five outbreaks of food poisoning due to cadmium, involving at least 50 persons. The syndrome was characterized by violent acute gastritis, occurring almost immediately after the ingestion of contaminated food. The cadmium responsible for the outbreak was found in liquids and in food preparations which had come in contact with cadmium-plated utensils. The cadmium metallic coating on the utensils was found to be soluble when placed in contact with solutions of dilute acetic acid and other organic acids commonly found in foods. Resulting organic cadmium salts were formed, which when taken internally produced poisonous cadmium chloride when combined with the hydrochloric acid of the gastric juice. It would seem highly important that the plating industry be made cognizant of the fact that cadmium is not a suitable substance for the plating of utensils used for food.

The possible harmful effects of karaya gum and other bulky materials frequently used therapeutically were investigated by Hoelzel, DaCosta and Carlson.<sup>334</sup> These investigators cite the results of previous experiments by Ivy and Isaacs, who reported an absence of intestinal lesions in albino rats fed 1 Gm. of karaya gum daily for ninety-one days. In the present study a large number of animals were given somewhat larger doses of the gum for a longer period. Hooded rats appeared to be more susceptible than albino rats to the development of lesions of the lower portion of the bowel. Serious intestinal lesions were encountered in 3 of 5 hooded rats who were fed large amounts of karaya gum for long

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332. Lemman, W. T., and Paschal, G. W., Jr.: Rupture of the Stomach Following Ingestion of Sodium Bicarbonate, *Ann. Surg.* **114**:997, 1941.

333. Frant, S., and Irving, K.: Cadmium "Food Poisoning," *J. A. M. A.* **117**:86 (July 12) 1941.

334. Hoelzel, F.; DaCosta, E., and Carlson, A. J.: Production of Intestinal Lesions by Feeding Karaya Gum and Other Materials to Rats, *Am. J. Digest. Dis.* **8**:266, 1941.

periods. The animals were fed diets which included granular karaya gum, bran or a poor grade of psyllium seed. Whether such results can be applied to the use of these substances in human beings remains to be seen. Fantus and his associates<sup>335</sup> have attempted to prove that bran has no harmful effect in human beings and provide a series of reports on this subject. Numerous stool examinations were first carried out to obtain some measure of colonic irritability, particularly on the basis of the content of mucus and leukocytes. Bran when added to an uncontrolled diet appeared to cause a softening and an increase in the weight of the stools. There was an increase in the volatile fatty acids, chiefly acetic and butyric acids, but there appeared to be no consistent correlation between this change and the laxative action associated with the ingestion of bran. The authors conclude that no conclusive evidence exists that bran causes or increases irritation of the bowel. The stool abnormalities which were occasionally noted, due to an increase in mucus, were attributed to other causes. A reasonable criticism of such conclusions seems proper. All of the experiments were made on healthy persons with no complaints referable to the bowel. The use of bran as a therapeutic agent has long been advocated as a corrective measure in patients with bowel disorders commonly known as "constipation." There can be no doubt that in many such instances, in patients with "irritable colon," "mucous colitis," etc., in whom constipation is a common clinical feature, the use of bran frequently causes an aggravation of existing symptoms.

Morgan<sup>336</sup> adds his protest against the use of liquid petrolatum to those of certain other investigators. According to this author, liquid petrolatum frequently causes symptoms, such as anorexia, indigestion, flatulence, fatigue, nervousness, dyschesia and anal leakage. In addition, he refers to the fact that it seriously interferes with the utilization of carotene, vitamin A concentrates and fat-soluble vitamin D. Such an indictment of a popular remedy is probably justified in part, although it is to be doubted that under ordinary conditions effects really deleterious to the health of the patient are encountered after its use.

As an unusual and curious observation the article by Felsen<sup>337</sup> on the sigmoidoscopic diagnosis of periarteritis nodosa should be mentioned.

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335. Fantus, B.; Wozasek, O., and Steigmann, F.: Studies on Colon Irritation: Examination of Feces, *Am. J. Digest. Dis.* **8**:296, 1941. Fantus, B., and Frankl, W.: The Mode of Action of Bran: I. Effect of Bran upon Composition of Stools, *J. Lab. & Clin. Med.* **26**:1774, 1941. Fantus, B.; Wozasek, O., and Steigmann, F.: Studies on Colon Irritation: Effect of Bran, *Am. J. Digest. Dis.* **8**:298, 1941.

336. Morgan, J. W.: The Harmful Effects of Mineral Oil (Liquid Petrolatum) Purgatives, *J. A. M. A.* **117**:1335 (Oct. 18) 1941.

337. Felsen, J.: Sigmoidoscopic Diagnosis of Periarteritis Nodosa, *Ann. Int. Med.* **15**:251, 1941.

The accurate description of the arterial lesions noted in the rectum and the rectosigmoid portion of the colon is excellent.

Gastrointestinal complaints due to various allergic manifestations are reported in detail by Thomas and Wofford<sup>338</sup> on the basis of 134 cases. The vague nature of the symptom complex is one of the distinguishing features, together with the fact that associated allergic manifestations were present in 90 per cent of cases. There was an 84 per cent incidence of familial allergy.

A complete review of the roentgenologic literature for 1940 as it pertains to the digestive tract is presented by Feldman.<sup>339</sup> The article is of particular value to those interested in the subject because of the well arranged bibliography that is appended to the comments on individual articles and serves as an excellent basis for reference.

Greater use is being made of peritoneoscopy as a diagnostic procedure in properly selected cases. Three hundred and fifty observations are reported in three papers by Walker and Playfair,<sup>340</sup> Olim<sup>341</sup> and Garrey.<sup>342</sup> The data presented by these authors justify the use of the procedure and the assertion that it will save many patients the risk and discomfort of an open abdominal exploration. It has been found to be of particular use in the evaluation of gastric and hepatic conditions and in the diagnosis of peritoneal and of pelvic disease. With care adequate biopsy material can be obtained without undue risk. It would seem that this method has now properly been added to other well established procedures as a safe, economical and reasonably accurate means of obtaining information in properly selected cases.

*War Medicine.*—The importance of gastrointestinal diseases and complaints in the present emergency is discussed in full by Pepper.<sup>343</sup> He presents statistics of diseases encountered among soldiers in the United States Army during the mobilization period from 1917 to 1919 as a basis for a comparison with the expected morbidity and mortality in the present conflict. The most frequent causes of hospitalization in this

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338. Thomas, J. W., and Wofford, C. P.: Gastro-Intestinal Allergy: A Review of One Hundred and Thirty-Four Cases, *Am. J. Digest. Dis.* 8:311, 1941.

339. Feldman, M.: A Clinical Roentgenological Review of the Literature for 1940, Pertaining to the Digestive Tract, *Am. J. Digest. Dis.* 8:279, 1941.

340. Walker, R. M., and Playfair, P. L.: Peritoneoscopy: Report Based on One Hundred and Twenty-Five Cases, *Lancet* 1:159, 1942.

341. Olim, C. B.: Peritoneoscopy: Analysis of One Hundred and Fifty Cases, *Surgery* 10:391, 1941.

342. Garrey, W. E.: Evaluation of Peritoneoscopy with Particular Reference to Diagnosis of Abdominal Tumors, *New England J. Med.* 225:180, 1941.

343. Pepper, O. H. P.: Disease Expectancy in the New Army, *War Med.* 1:463 (July) 1941.

group of over 2,250,000 men for definite diseases of the digestive tract are recorded as follows: ulcer of the stomach, 1,201; duodenal ulcer, 884; appendicitis, 21,689; hernia, 35,535; other diseases of the stomach, 29,271; other diseases of the intestines, 54,665; diarrhea, enteritis and colitis, 38,355, and diseases of the liver and the gallbladder, 6,443. As Pepper states, this group is of no mean importance and there is little reason to believe that there will be any lessening in the frequency of peptic ulcer; in fact, there is likely to be a definite increase, if rumors concerning the frequency of this condition in the armed forces of other countries can be believed. He is also correct in the following statement:

As to the indefinite miscellaneous disorders of the stomach and of the intestines, diarrhea, enteritis and colitis, a marked improvement should be expected, proportionate to the better diet and even more to the more cleanly preparation of food which it is hoped will be the rule in the new Army. This factor is controllable to a great extent. If figures approaching those of the past are permitted to occur, it will be a disgrace. A lower incidence of intestinal infestations can also be part of the expectancy.

Because of the distribution of the armed forces it is to be anticipated, however, that there may be a tremendous increase in the incidence of tropical diseases, including the various forms of dysentery, which, however, should be amenable to successful treatment, as indicated in the earlier part of this review. Because of the magnitude of the problems and strains involved in modern mechanized warfare, it is apparent also that various disorders which are more or less conditioned by varying degrees of nervous strain and by adequacy of diet will be encountered in important numbers. The peptic ulcer problem may be minimized by the proper exclusion of known patients with ulcer from the combat forces. It is inevitable, however, that numerous persons, particularly in the enlisted personnel, will be inducted into service without the discovery of a quiescent ulcer.

The importance of the ulcer problem has been already noted in previous reports appearing in the European literature and is reaffirmed in an article by Urquhart, Singleton and Feasby,<sup>344</sup> who comment on the frequency of duodenal ulcer among the Canadian forces. In the group of cases under discussion by these authors, symptoms of ulcer developed in 90 per cent within the first six months of service in England. In about one third of the cases the patients gave histories of no previous gastric disturbances. In this article there is also an excellent discussion of the incidence of dyspeptic symptoms. An intelligent evaluation of these symptoms made it possible to keep the majority of these "functional dyspeptics" on active duty.

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344. Urquhart, R. W. I.; Singleton, A. C., and Feasby, W. R.: The Peptic Ulcer Problem, *Canad. M. A. J.* **45**:391, 1941.



A complete discussion concerning the methods of the examination and disposition of persons with gastrointestinal symptoms is presented by Schindler,<sup>345</sup> who considers a large variety of conditions, in addition to gastritis. The author classifies for ultimate disposition and treatment most of the important disorders in an intelligent and comprehensive fashion. In the preparation of his article he has taken advantage of broad clinical experience derived by himself and others during the last war. He stresses the importance of obtaining objective evidence in individual cases, rightly claiming that this is much more important than any "impression" a military surgeon may derive from a careful history. This is particularly true when it is necessary to rule out malingering. He makes a particularly intelligent attempt to evaluate the possible activities that may be permitted to patients suffering from various disorders that may incapacitate them for combat duty.

The Army's nutritional problems are fully discussed by Tobey,<sup>346</sup> with especial attention to measures for situations such as those that arise during tank movements, parachute work and aviation activities. In such forms of mobile combat, concentrated rations are important and are duly considered.

The importance of abdominal distention in the production of annoying or even dangerous symptoms as it relates to the problems of aviation is discussed by Vega<sup>347</sup> and by Collins.<sup>348</sup> The great increase in the volume of gastrointestinal gases at high altitudes may result in a forcing upward of the diaphragm with striking alteration in respiration, associated with a diminution of vital capacity, alveolar oxygen tension and carbon dioxide tension. Respiration approaching that of the Cheyne-Stokes type, according to Vega, may be noted because of undue abdominal distention. An unusual manifestation of such a condition is reported by Collins in a patient with congenital idiopathic dilatation of the colon. This person while flying at 14,000 feet (4,200 meters) experienced considerable abdominal distention, dyspnea and precordial pain, which were relieved when the plane descended to normal barometric levels or when large amounts of flatus were passed.

Visceral injury caused by compression or suction waves set up by the detonation of high explosives on land or at sea is described by

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345. Schindler, R.: *Gastroenterology in the Army: Methods of Examination and Disposition of Cases*, War Med. **2**:263 (March) 1942.

346. Tobey, J. A.: *The Army's Nutritional Problems*, War Med. **2**:437 (May) 1942.

347. Vega, M. G.: *Changes in Respiration and in the Digestive Apparatus at High Altitudes*, Medicina, Madrid **9**:162, 1941.

348. Collins, L. H.: *Excessive Abdominal Distention at High Altitudes in a Case of Congenital Megacolon (Hirschsprung's Disease)*, J. A. M. A. **117**: 1012 (Sept. 20) 1941.

Breden and his colleagues.<sup>349</sup> Organisms permeating a contused colon were the cause of pelvic and subphrenic abscesses in 2 patients. Seven patients had severe melena but without serious complications, and 1 patient suffered fatal injury associated with laceration of the ileum and peritonitis due to compression. In the last-mentioned patient section of the ileum showed diffuse hemorrhages in the submucous and subperitoneal layers, which were similar to those discussed in a previous article, as a result of abdominal trauma. In all likelihood, the mechanism involved was quite analogous. In the surviving patients the immediate symptoms of vomiting with blood, diarrhea with melena and testicular pain occurring after sudden compression were not severe. Conservative therapy was advocated.

Massachusetts General Hospital.

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349. Breden, N. P.; d'Abreu, A. L., and King, D. P.: Sudden Compression Injuries of Abdomen at Sea, *Brit. M. J.* **2**:144, 1942.

## News and Comment

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American Association for the Advancement of Oral Diagnosis.—The annual meeting of the American Association for the Advancement of Oral Diagnosis, which was scheduled to be held November 12 and 13 in Boston, has been canceled and will not be held in 1942.

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### CORRECTIONS

On page 58 of the article "Stenosis of the Infundibulum" by Drs. Maurice Lev and Sidney Strauss, in the July issue (*ARCH. INT. MED.* **70**:53, 1942), the second sentence of the section entitled "Comment" should read "When the patient was first seen, ten years before death, a systolic murmur was heard at the base of the heart." Similarly, in the last paragraph under this heading, "the base of the left lung" should read "the base of the heart."

In lines 17 and 21 on page 58, "the P wave in lead II" should read "the second pulmonic sound."

In the article by Dr. Harry D. Leinoff, "Acute Coronary Thrombosis in Industry: I. Direct Nonpenetrating Injuries, with Report of Cases," in the July issue (**70**:33, 1942) lead I in figure 4, on page 47, is upside down and indicates, erroneously, that the T wave was upright, instead of being inverted and coved.

## Book Reviews

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**Arthritis in Modern Practice: The Diagnosis and Management of Rheumatic and Allied Conditions.** By Otto Steinbrocker, M.D., with special chapters by John G. Kuhns, M.D., F.A.C.S. Price, \$8. Pp. 606, with 321 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The problems of arthritis are receiving greater and greater attention from members of the medical profession throughout the country, as evidenced by organizations for the study of arthritis, by articles in current medical literature and by the recent appearance of several books devoted entirely to the subject of arthritis, of which the volume under review is one. This attention to a crippling and disabling disorder which probably is as responsible as any one disease for physical disability and mental suffering is well warranted. Too long have arthritic patients been pushed from pillar to post because of the unsatisfactory results that have been usually obtained by physicians in the management of them.

This book is prepared by Steinbrocker, chief of the arthritis clinic of Bellevue Hospital, New York, and in addition to the nineteen chapters that he devotes to the subject, there are five chapters on painful feet; posture and exercise; splints and supports; manipulation, treatment and operation, and surgical procedures written by Dr. Kuhns, chief of the orthopedic and surgical service of the Robert Breck Brigham Hospital, Boston.

The senior author has devoted the greatest number of pages, naturally, to rheumatoid arthritis. The chapter on this form of arthritis is a clear, concise, authoritative statement of the most frequent cause of disabling joint injuries. It is to be commended highly. The senior author, incidentally, devotes some pages to gold therapy but refuses to commit himself as to the efficacy of this type of treatment.

The succeeding chapters have to do with other types of arthritis, such as hypertrophic arthritis, gout and infectious arthritis. He devotes chapters to painful shoulder, backache, sciatica and other conditions with which a person who is treating arthritis should be familiar, as well as to physical therapy.

This book compares favorably indeed with any and all books on arthritis. It can be recommended. It is well printed, and the numerous illustrations, on the whole, are clear. Altogether, it is pleasing in appearance.

**Diseases of Metabolism.** Edited by Garfield G. Duncan, M.D., Associate Professor of Medicine, Jefferson Medical College. Price, \$12. Pp. 985, fully illustrated, with 7 plates in color. Philadelphia: W. B. Saunders Company, 1942.

The scope of this book is contained in the editor's definition of metabolism—"Metabolism is the sum total of tissue activity as considered in terms of physicochemical changes associated with and regulated by the availability, utilization and disposal of protein, fat, carbohydrate, vitamins, minerals, water and the influences which the endocrines exert on these processes."

To present the fundamental knowledge of metabolism, namely, its physiology, physicochemistry and pathologic physiology; to apply this knowledge to the explanation of diseases of metabolism, and to outline a rational basis for the treatment of these diseases is no mean task.

A brief foreword by Sir Frederick Banting was epically enough received by the editor but a few days before Sir Frederick's untimely death.

The editor has wisely chosen a group of outstanding authorities to assist him. Carbohydrate Metabolism is presented by C. N. H. Long; Protein and Lipid Metabolism, by Abraham White; Mineral Metabolism and Melituria, by Abraham

Cantarow; Water Balance in Health and in Disease, by John P. Peters; Nutritional and Metabolic Aspects of Disorders of the Blood, by Leandro M. Tocantins; Vitamins and Avitaminoses, by Tom D. Spies and Hugh R. Butt; Undernutrition, by L. H. Newburgh; Obesity, by Frank A. Evans; Xanthomatoses, by Edward Mason, and Gout, by Walter Bauer and Friedrich Klemperer. The editor, Garfield G. Duncan, covers Hyperinsulinism, Diabetes Insipidus and Diabetes Mellitus.

The style of each author is uniformly excellent. As the advances in the fundamentals of metabolism have been so revolutionary in the last fifteen years, no medical student, general practitioner or internist could but profit immeasurably by reading this book. The reviewer is willing to predict that the book will become a classic in its field.

**Religion in Illness and Health.** By Carroll A. Wise. Price, \$2.50. Pp. 279. New York: Harper & Brothers, 1942.

Dr. Wise has formulated an approach to religion that embodies and brings to articulate expression many of the ideas implicit in religious teachings, regardless of individual creed. Because of this, his book satisfies a need which many persons had long felt but which had remained unsatisfied because of inability to give it overt expression in words. It is a strange experience to see the fundamental principles of religious teachings expressed in the terminology and concepts of psychiatry, psychology and psychoanalysis; yet this is the unique contribution of the book—a contribution which renders it of particular value and interest to professional groups.

Although the word psychobiology is never used by the author, an exposition of the "organismic approach" is given in Chapter IV, in which the concepts presented are essentially the concepts of psychobiology.

Despite some awkwardness of style and organization the author shows an insight into human behavior that can come only from broad psychiatric and psychologic training and experience. Yet one of the strongest points in the book is Dr. Wise's development of his concept of the role of the clergyman in dealing with problems of mental health. He believes that the clergyman's psychiatric training enables him to define his own sphere of activity as one distinct and different from that of the psychiatrist, but one requiring whole-hearted cooperation with the psychiatrist in the interest of the patient's mental health and well-being.

**From Witchcraft to Chemotherapy: The Linacre Lecture 1941.** By Sir Walter Langdon-Brown. Price, \$0.60. Pp. 60. London: Cambridge University Press, 1942.

This scholarly and entertaining essay would only be spoiled by any attempt at a critical review. It is full of interest to the medically trained man and to the lay reader and can be unreservedly recommended to both as conforming to the best ideal of English medical essays.

**Synopsis of Materia Medica, Toxicology and Pharmacology.** By Forrest Ramon Davison. Second edition. Price, fabrikoid, \$5.75. Pp. 695, with 45 illustrations. St. Louis: C. V. Mosby Company, 1942.

The second edition of Dr. Davison's well known book is much like the first edition, although important additions and deletions have been made. The material on the sulfanilamide drugs has necessarily been enlarged. This book is useful for desk reference.

# ARCHIVES of INTERNAL MEDICINE

VOLUME 70

NOVEMBER 1942

NUMBER 5

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## INCOMPLETE RUPTURE OF THE AORTA

A HERETOFORE UNRECOGNIZED STAGE OF DISSECTING ANEURYSM AND  
A CAUSE OF CARDIAC PAIN AND CARDIAC MURMURS

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Dissecting aneurysm has been recognized at autopsy for many years, and more recently the clinical signs and symptoms of that condition have become sufficiently well established for the diagnosis to be made ante mortem in a fairly large number of cases. In most instances actual dissection is preceded by a tear of the intima, through which the column of blood gains access to the media to cause dissection. Not infrequently dissection does not occur immediately after the intimal tear, and the tear may heal by the formation of scar tissue, leaving a defect in the aortic wall. This early stage without dissection has not been recognized clinically, however, and has seldom been recognized as such at autopsy. Clinical recognition of incomplete rupture is important in that actual dissection may be prevented or postponed in some cases. Its manifestations are dramatic enough and the condition is common enough for the correct diagnosis to be made ante mortem in some instances.

### CHARACTER OF THE LESION

Incomplete tears are usually encountered in the ascending portion of the aortic arch, at or near one of the commissures. In most instances they are transverse, but occasionally they are oblique and rarely longitudinal. The size of the tears varies considerably, but they are usually 0.5 to 2 cm. in length. Because of the gaping which occurs, they are usually elliptic, and their edges are sharp and clearly defined. The lips of a tear are usually 3 to 6 mm. apart, and between the lips the base tends to bulge outward slightly, usually less than a centimeter. The base is usually smooth, white and glistening and may show slight trabeculation.

Microscopic sections across the tears show an abrupt interruption of the media involving approximately the inner two thirds of that coat (fig. 1). Breaking and fraying out of the elastica can be demonstrated

From the Department of Pathology, George Washington University School of Medicine.

by Weigert's stain or other stains specific for elastic tissue (fig. 2). The intima is usually thickened and hyaline at the base of the tears, and there is scar tissue in the disrupted media. Not uncommonly lymphocytes and plasma cells are encountered in the bases of recent

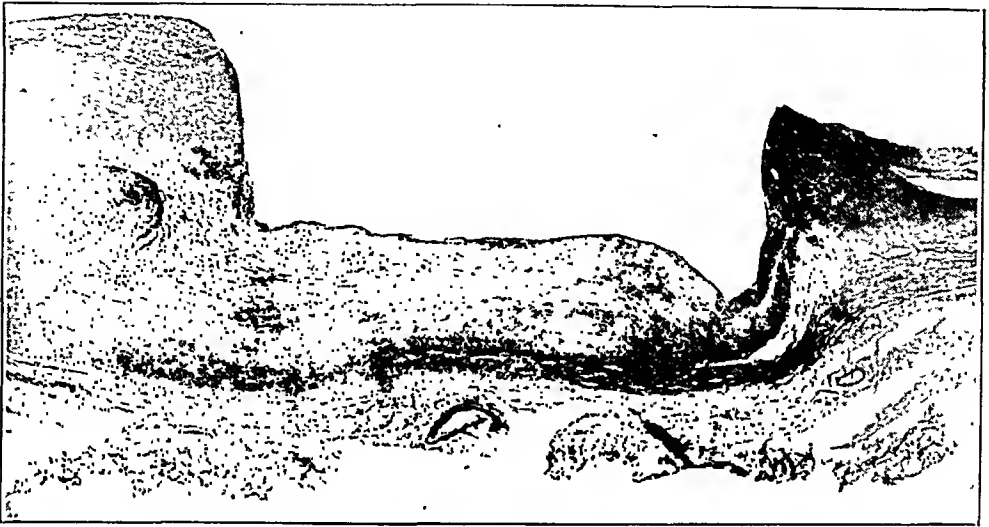


Fig. 1 (case 5).—Cross section of an incomplete rupture of the aorta, showing an abrupt break of the media and proliferation of fibrous tissue in the base of the tear. Hematoxylin and eosin;  $\times 17$ .

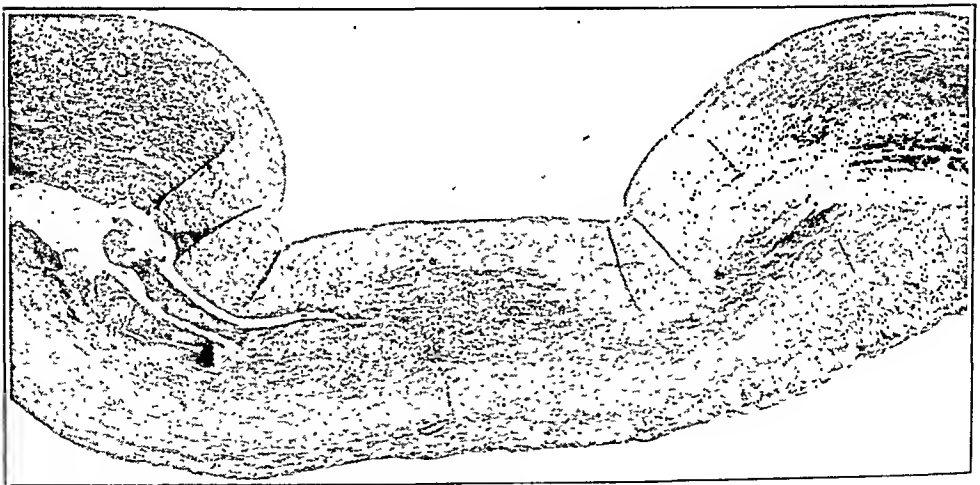


Fig. 2 (case 9).—Cross section of an incomplete rupture of the aorta, showing disruption of elastic fibers at the edges and the base of the tear. The split in the media shown at the left represents dissection arising from another intimal tear. Weigert's stain for elastic tissue;  $\times 10$ .

tears. These are believed to be part of the healing process and are not thought to represent specific inflammatory changes. The media may appear perfectly normal a few millimeters back from the edges of a

tear. In an exceptional case in this series mucoid changes have been noted in the media, but since they were usually found only at or near the tear, they were taken to be degenerative changes which followed the tear.

In recent lesions the edges are so sharp, straight and clearcut that a pathologist is apt to believe that they are artefacts made with knife or scissors. Particularly is this true if the aorta is cut off shortly above the aortic ring, as is frequently done.

#### FREQUENCY

If one judges the frequency of incomplete rupture of the aorta by the number of cases recorded in the literature, one must conclude that the condition is rare. In the American literature incomplete tear is occasionally referred to in cases of dissecting aneurysm, but no reference could be found to incomplete tear as such. Gallavardin and Gravier<sup>1</sup> and Maresch<sup>2</sup> indicated that incomplete tear of the aorta is not uncommon and expressed the belief that it is frequently overlooked at autopsy. Furthermore, in many instances complete aortic rupture probably takes place through the base of an old tear and obliterates the autopsy evidence of its previous existence. Since 1935 6 cases of incomplete rupture of the aorta without dissecting aneurysm have been encountered. Several incomplete tears in cases in which death was due to dissecting aneurysm have also been noted, the dissection occurring through a separate tear in the aorta. In the same period 2 cases of dissecting aneurysm have been studied in which the clinical record strongly suggests that the process occurred in two stages. This makes a total of 8 cases in about 1,600 autopsies on patients of all ages, and 3 additional cases have been encountered in a review of autopsy records. The services from which these figures are derived<sup>3</sup> have shown a high incidence of hypertension, and it is likely that the proportion would be lower in areas where hypertension is less frequent.

Incomplete rupture has been much more frequent in this series than has rupture of an aortic valve cusp, if cases of endocarditis are excluded.

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1. Gallavardin, L., and Gravier, L.: Rupture incomplète de l'aorte: Insuffisance aortique fonctionnelle consécutive, *Paris méd.* **45**:29, 1922.

2. Maresch, R.: Zur Kenntnis der Insuffizienz der Aortenklappen, *Wien. klin. Wchnschr.* **42**:417, 1929.

3. Cases 1, 2, 3, 4, 6 and 7 were encountered in the Pathology Service of the Medical College of the State of South Carolina, Charleston, and are used in this report with the consent of Dr. Kenneth M. Lynch, professor of pathology. Cases 5, 8, 9, 10 and 11 were encountered in the Pathology Service of the George Washington University School of Medicine and are used with the consent of Dr. Roger M. Choisser, professor of pathology.



Yet the diagnosis of rupture of an aortic valve cusp is occasionally made ante mortem by expert cardiologists.

#### PREDISPOSING FACTORS

As in the case of dissecting aneurysm, the essential factor predisposing to incomplete rupture is severe hypertension, usually of long duration. One cannot be certain that there is any definite abnormality of the walls of the aorta prior to the occurrence of the tear. Microscopic examination of sections from the aorta taken near the lesion but not including it usually do not show any recognizable abnormality. Atherosclerosis is probably not a cause for this condition, since the tears seldom occur through an atheromatous plaque or ulcer. Syphilitic aortitis is not commonly found in association with these tears and does not appear to be an etiologic factor. It is possible that *medionecrosis aortae idopathica cystica* of Erdheim may be present in some cases, but this has also not been noted frequently.

Since most of the tears occur in the proximal portion of the ascending aorta, it is extremely likely that there is a local predisposition in this area. The valve commissures exert a rocking force and pull on the aortic wall as they are driven shut in diastole by the column of aortic blood, and this local force is probably the cause for the more frequent occurrence of tears at this point. The fact that the tears are usually transverse to the axis of the valve commissures adds weight to this hypothesis.

#### PRECIPITATING FACTORS

In some instances rupture occurs during straining or exertion, although this is not always the case. Presumably the blood pressure is raised to a still higher level by such acts, and this may in itself be the immediate cause of the tear.<sup>4</sup> Or it may be that the fixation of the diaphragm and the increased intrathoracic tension in some way fix the aorta, so that there is a greater tendency toward rupture.

In some instances actual trauma, usually to the chest, has precipitated a tear. In a case reported by Heller<sup>5</sup> rupture apparently occurred when a heavy burden fell on the patient's chest. In the case reported by Oppenheim<sup>4</sup> clinical manifestations followed a blow by a falling piece

4. Oppenheim (Gibt es eine Spontanruptur der gesunden Aorta und wie kommt sie zustande? München. med. Wchnschr. 45:1234, 1918) experimented with human aortas and concluded that a pressure of approximately 2,000 mm. of mercury was required to rupture a normal aorta. In his experiments a pressure hose was directed into the aortic orifice through the left ventricle and held tightly just below the aortic valve. It seems likely that rupture would have occurred at a lower pressure if the systolic and the diastolic pressure had been simulated by alternately raising and lowering the pressure, permitting the column to pound back on the aortic valve cusps.

5. Heller, A.: Ueber ein traumatisches Aortenaneurysma und traumatische Insuffizienz der Aortenklappen, Deutsches Arch. f. klin. Med. 79:306, 1904.

of granite. Nordlander<sup>6</sup> reported a case in which a fatal rupture occurred while the patient was at work. Nordlander and Oppenheim both referred to the occurrence of ruptured aorta in aviators falling from a high altitude.

#### IMMEDIATE CLINICAL MANIFESTATIONS

Probably the most common symptom caused by incomplete rupture of the aorta is a choking sensation or a feeling of suffocation. Dyspnea may come on suddenly and continue for some time. Pain is also a frequent symptom and may be "stabbing" or "tearing," although pain is less frequent and less severe than when dissection supervenes immediately.

Occasionally cough, hemoptysis and fever are the presenting symptoms and may be associated with pain of pleuritic type. Under such circumstances physical examination and roentgen study may show evidence of pneumonic consolidation. Wood and associates<sup>7</sup> and Hardaway and Green<sup>8</sup> have reported cases of such an occurrence, and another is added here (case 11). At autopsy the pulmonary changes are found to be due to areas of atelectasis. The clinical diagnosis under these circumstances would undoubtedly be difficult.

The temperature and the leukocyte count are usually moderately elevated for a few days, and the pulse and the respiratory rate are frequently accelerated.

On examination enlargement of the heart and hypertension are usually evident. The most important physical finding is undoubtedly the presence of heart murmurs. These may be either systolic or diastolic and are usually best heard in the aortic area. The systolic murmur is usually harsh and is probably due to vibration in the blood current of the abrupt, shelflike edges of the tear or to eddying of blood over the small pouch between the lips of the tear. The diastolic murmur, when present, is due to actual aortic insufficiency, as will be explained subsequently.

Roentgen examination of the chest usually shows widening of the aortic arch, but it has been impossible, even in retrospect, to read any pathognomonic sign into the picture in the chest.

An electrocardiogram usually shows left axis deviation but nothing else. In an occasional case in which a tear involves the mouth of a

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6. Nordlander, T. A.: Partially Healed Spontaneous Rupture of the Aorta, *Tr. Chicago Path. Soc.* **12**:123, 1925.

7. Wood, F. C.; Pendergrass, E. P.; and Ostrum, H. W.: Dissecting Aneurysm of the Aorta with Special Reference to Its Roentgenographic Features, *Am. J. Roentgenol.* **28**:437, 1932.

8. Hardaway, R. M., and Green, M. M.: Intrapericardial Rupture of Aorta, *Am. Heart J.* **10**:384, 1935.

coronary artery there may be signs of coronary insufficiency, but usually the electrocardiogram is of diagnostic value for what it does not show.

Probably the usual outcome is the subsidence of pain and dyspnea within a day or two, followed by a longer period of weakness, easy fatigue or a realization that all is not well. In a considerable proportion of cases, however, dissection of the aorta occurs days, weeks or months later, with the usual manifestations of that condition. In other cases the clinical picture becomes one of aortic regurgitation with congestive heart failure.

#### EFFECTS OF INCOMPLETE RUPTURE OF AORTA

The subsequent course in cases of intimal tear apparently depends on two factors: (1) the position of the tear in relation to the commissures of the aortic valve, and (2) whether dissection occurs.

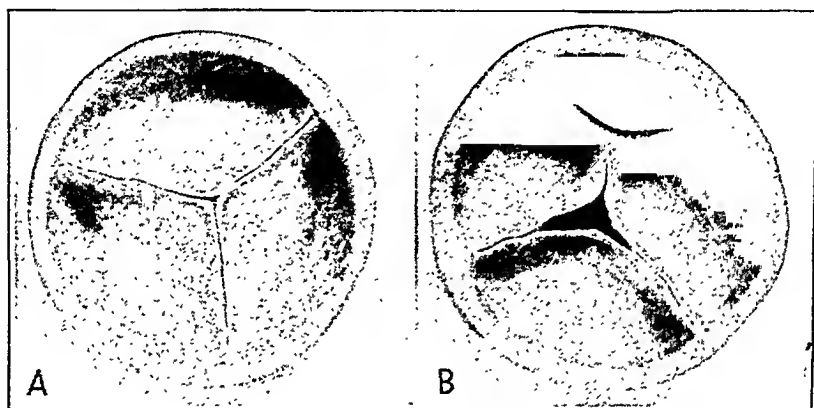


Fig. 3.—Wax models of the aortic valve, showing the mechanism of aortic insufficiency in case of an incomplete tear at a commissure of the valve. Aortic insufficiency in cases of dissecting aneurysm is probably due to the same mechanism. *A*, a normal aortic valve viewed from above. *B*, aortic insufficiency due to an incomplete tear in the aortic wall with loosening of the affected aortic valve commissure.

If dissection does not occur and the tear is well above the aortic commissures, healing will usually take place. There is then no cardiac embarrassment, but the local lesion remains as a point of weakness in the aorta, and subsequently complete tear may occur through this area and obliterate the evidence of a two stage process. Or with continued hypertension tears may occur in other areas; multiple small tears are not an uncommon incidental finding at autopsy.

But if the tear is at or just above a commissure and transverse to it, aortic insufficiency will result and may lead to death from congestive heart failure. Under such circumstances, as the tear gapes, the commissure loosens and the corresponding cusps hang at a lower level in the aortic ring than the unaffected one and valvular incompetence results (fig. 3). Murmurs and other signs of aortic insufficiency are not

uncommon in cases of dissecting aneurysm,<sup>9</sup> but such manifestations are usually dependent on the initial intimal tear being at and transverse to a commissure of the aortic valve.<sup>10</sup>

Without regard to the position of the original intimal tear dissection may come on within a few hours or probably can even occur years later. The clinical picture is then that of dissecting aneurysm with which cardiologists are familiar. Usually the subsequent dissection is short, with rupture into the pericardial sac and sudden death from cardiac tamponade. In such cases the dissection may destroy all evidence that an incomplete tear preceded the dissection by an appreciable interval. Clinical histories frequently suggest that the dissection occurred in several stages, and the recognition of cases of incomplete tear without dissection seems to furnish the "missing link" in this concept.

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9. (a) Chiari, H.: Ueber die Differenz im mikroskopischen Befunde bei ausgeheilten Aortenrissen entstandenen und bei "spontanen" Aortenaneurysmen, *Verhandl. d. deutsch. path. Gesellsch.* 7:180, 1904. (b) Letulle, M.: Anévrisme disséquant étendu à la totalité de l'aorte et spontanément guéri, *Bull. et mém. Soc. méd. d. hôp. de Paris* 22:1045, 1905. (c) Roemer, R.: Ueber zwei Fälle von spontaner Querruptur der Aorta bei Aorteninsuffizienz, *Inaug. Dissert.*, Erlangen, 1906. (d) MacCallum, W. G.: Dissecting Aneurysm, *Bull. Johns Hopkins Hosp.* 20:9, 1909. (e) Uhles, B.: Ueber einen Fall von Aortenruptur mit Blutung in die Perikardhöhle, *Med. Klin.* 20:49, 1924. (f) Resnik, W. H., and Keefer, C. S.: Dissecting Aneurysm with Signs of Aortic Insufficiency, *J. A. M. A.* 85:422 (Aug. 8) 1925. (g) Hall, E. M.: Healed Dissecting Aneurysm of Aorta, *Arch. Path.* 2:41 (July) 1926. (h) Hamilton, W. F., and Abbott, M. E.: Coarctation of the Aorta of the Adult Type, *Am. Heart J.* 3:381, 1928. (i) Lundberg, Å.: Three Cases of Healed Aortic Rupture, *Acta med. Scandinav.* 73:19, 1930. (j) Klotz, O., and Simpson, W.: Spontaneous Rupture of the Aorta, *Am. J. M. Sc.* 184:455, 1932. (k) Narr, F. C., and Wells, A. H.: Rupture of the Aorta, *Am. Heart J.* 8:834, 1933. (l) Hamman, L., and Apperly, F.: An Instance of Spontaneous Rupture of the Aorta with Aortic Insufficiency, *Internat. Clin.* 4:251, 1933. (m) Hamburger, M., Jr., and Ferris, E. B., Jr.: Dissecting Aneurysm, *Am. Heart J.* 16:1, 1938. (n) Roberts, J. T.: Medionecrosis Aortae Idiopathica Cystica, *ibid.* 18:188, 1939. (o) Gouley, B. A., and Anderson, E.: Chronic Dissecting Aneurysm of the Aorta, Simulating Syphilitic Cardiovascular Disease, *Ann. Int. Med.* 14:978, 1940. (p) Dissecting Aneurysm of Aorta, Cabot Case 27292, *New England J. Med.* 225:116, 1941. (q) Dissecting Aneurysm of Aorta with Rupture into Pericardium, Cabot Case 27302, *ibid.* 225:155, 1941.

10. In some instances in which diastolic murmurs have been noted at the aortic area no tear has been found near the commissures, but dissection has extended proximally in the media of the vessel, so that the attachments of the commissures are loosened and the effect is much the same as if an intimal tear had occurred at the commissures. Other explanations have been advanced for the insufficiency in cases of dissecting aneurysm—dilatation of the valve ring or a mechanism similar to that operative in arteriovenous fistula—but they seem inadequate when compared to the purely mechanical concept.

## HEALED AORTIC TEAR ENCOUNTERED INCIDENTALLY AT AUTOPSY

Chiari<sup>9a</sup> stated in 1904 that he had 4 specimens showing healed aortic tear in his museum. Asahi<sup>11</sup> reported a case in which a healed tear was found in the aorta, well above the aortic cusps, in a patient who died of pulmonary tuberculosis. Nordlander<sup>6</sup> stated that cases in which there was autopsy evidence of healed aortic rupture were encountered but that the clinical records usually did not reveal episodes to indicate when the tears occurred. He reported a case in which a healed tear was found in the aorta and in which death was a result of a separate dissecting aneurysm. Maresch<sup>2</sup> stated that shallow healed tears in the aortic walls were not uncommon in cases of hypertension and may not be associated with dissecting aneurysm.

CASE 1.—J. B., a 35 year old Negro, was brought to the hospital on Christmas Eve 1935 in a comatose state. His breath had a strong odor of alcohol. No examination was made. Death occurred five hours after admission. At autopsy the kidneys were small and showed evidence of sclerosis of the arterioles. The heart was hypertrophied. Examination of the brain disclosed a large pontile hemorrhage, with blood filling the ventricular system. Just above the aortic valve was an old healed transverse rent 2 cm. in length and gaping about 5 mm. Its base was thin and bulged outward slightly. Its edges were sharp, as if cut with a knife. Microscopically, there was moderate perivascular infiltration with lymphocytes and plasma cells. This lesion may have been one of syphilitic aortitis, although it did not have that appearance grossly. No medial necrosis was evident.

CASE 2.—P. B., a 45 year old Negress, was admitted to hospital Sept. 25, 1936 and died two hours after admission. The patient was comatose, and no history was obtained. The heart was enlarged, the apical impulse being in the sixth interspace 10 cm. to the left of the midline. The heart sounds were clear and regular. A loud systolic murmur was heard over the whole precordium, but no diastolic murmur was noted. The blood pressure was 255 systolic and 115 diastolic. There was a left hemiplegia. At autopsy there was a large hemorrhage in the right internal capsule, with extravasation into the subarachnoid space. The kidneys were small but showed little evidence of vascular disease. A short distance above one of the commissures of the aortic valve was a transverse rent in the aortic wall, bulging slightly outward (fig. 4). Its base was covered with scar tissue. The corresponding valve cusps appeared to hang slightly lower than normal in the aortic ring, but there was no definite insufficiency. No other abnormality could be found which might explain the heart murmur. There was no gross or microscopic evidence of syphilitic aortitis or of medial necrosis.

CASE 3.—A. B., a 45 year old Negro, was brought into the hospital in coma on March 23, 1937 and died twenty hours later. No history was obtained. The heart was enlarged downward and to the left. The heart sounds were distant, and no murmurs were heard. The blood pressure was 230 systolic and 150 diastolic. Autopsy disclosed hemorrhage into the cerebellum, with rupture into the fourth ventricle; the whole ventricular system was filled with blood. Microscopic sections

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11. Asahi, K.: Ueber die Differenz in mikroskopischen Befunde bei ausgeheilten Aortenrissen entstandenen und bei "spontanen" Aneurysmen der Aorta, *Ztschr. f. Heilk.* 6:163, 1905.

of the kidneys showed the necrotic arteriolar changes commonly attributed to "malignant" hypertension. A short distance above the cusps of the aortic valve was a healed transverse rent in the aortic wall, 1.5 cm. long and 5 mm. wide. The tear extended into the media slightly, and the base of the tear was crossed by several bands of torn media covered over with scar tissue. The cusps did not appear to sag, and the valve was thought to be competent. There was no evidence of syphilitic aortitis, either grossly or microscopically, and no medial necrosis was evident.

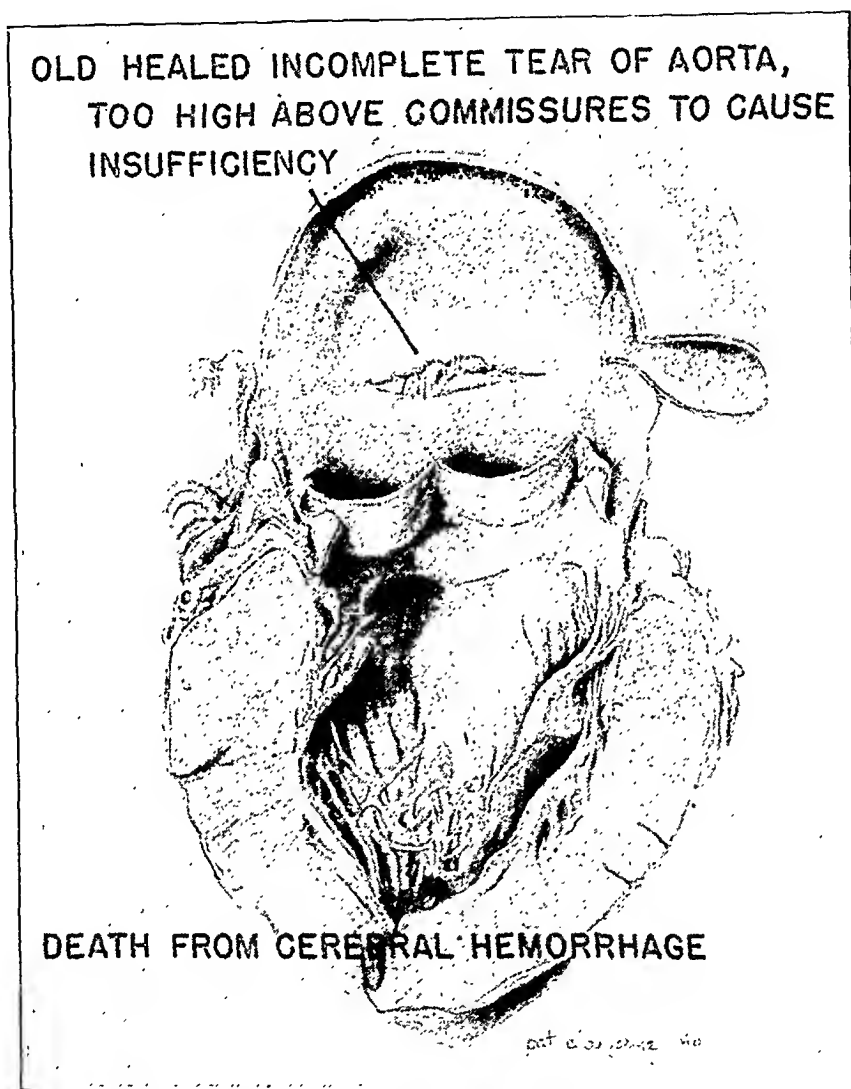


Fig. 4 (case 4).—Artist's drawing of the autopsy specimen. Note the abrupt edges of the tear and the bridging of the base of the defect with scar tissue. The duration of this tear is unknown.

CASE 4.—O. A., a 49 year old Negro, was admitted to the hospital in coma on Jan. 21, 1938 and died twenty-three hours later. The clinical diagnosis was hypertensive cardiovascular disease with cerebral hemorrhage. Autopsy disclosed evidence of hypertension in the kidneys and heart. A large area of hemorrhage was noted in the midbrain and extending into the right cerebral hemisphere. One centimeter above the aortic valve was a transverse slit 1.5 cm. in length in the intima and extending into the media. The tear gaped slightly, and its edges were sharp. Its

base was dense and gray and had a terraced appearance. The corresponding valve cusp did not appear lowered, and valvular insufficiency was thought not to be present. There was no evidence of syphilitic aortitis, either grossly or microscopically, and no medial necrosis was evident.

CASE 5.—C. R., a 59 year old white man, was seen by Dr. Leo Brown and Dr. Paul Dickens in November 1938 because of the frequent occurrence of epigastric pain after eating. The pain also came on with excitement. It did not radiate from the epigastrium. At that time the blood pressure was 210 systolic and 120 diastolic. The heart was enlarged, but no murmurs were noted. An electrocardiogram (fig. 5) was interpreted as showing evidence of myocardial damage, probably a result of

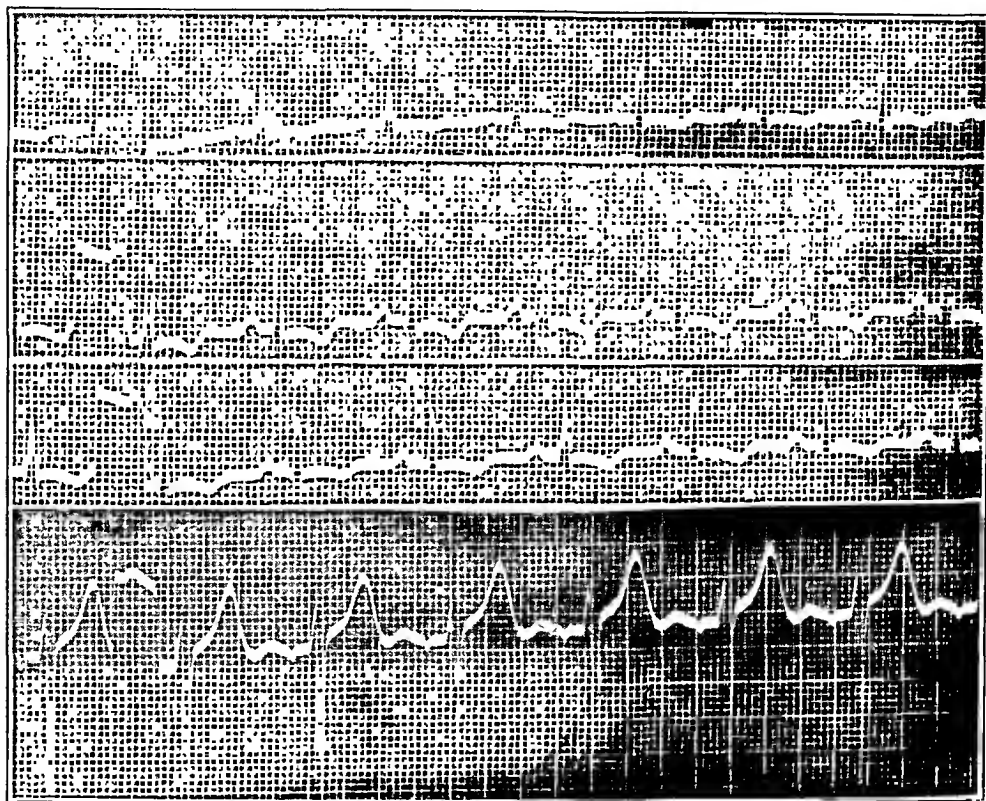


Fig. 5 (case 5).—An electrocardiogram, taken five months before death. Thrombosis of the interventricular branch of the left coronary artery was encountered at autopsy. There was an incidental healed incomplete tear in the aortic wall well above the commissures of the aortic valve.

coronary occlusion. The Wassermann reaction of the blood was negative. In May 1939 dyspnea on exertion developed, but edema was not noted. In June he was admitted to the hospital because of severe precordial pain and dyspnea. At that time the blood pressure was 180 systolic and 120 diastolic. No heart murmurs were noted. There was no edema. Death occurred two days later. At autopsy coronary heart disease was evident, and there was a recent myocardial infarct corresponding with the distribution of the interventricular branch of the left coronary artery. This vessel was completely occluded by a thrombus. In the ascending portion of the aortic arch, about 2 cm. above the aortic valve, there was a transverse rent in the aortic

wall extending into the media. Its base was white and scarred and bulged outward slightly. It was too high above the valve to have caused aortic insufficiency. Sections through the tear (fig. 1) showed round cell infiltration of the media and the adventitia suggestive of syphilis but probably a result of the healing of the tear. No medial necrosis was evident.

Unfortunately, in all but 1 of the cases just reported the patients were in coma when first seen, and it was impossible to interpret the aortic tears in the light of clinical symptoms which may have been noted. In the 1 case in which there was an adequate history the patient complained frequently of precordial pain, but the pain cannot be ascribed to the aortic lesion, since there was advanced disease of the coronary arteries. Hence, it is possible that this type of lesion—incomplete tear well above the aortic commissures without aortic insufficiency—does not produce significant symptoms. The symptoms given previously for incomplete rupture may be the symptoms of cardiac embarrassment from sudden aortic insufficiency. In order to clear up this point, it will be necessary to study the case histories of additional patients.

#### INCOMPLETE AORTIC RUPTURE CAUSING AORTIC INSUFFICIENCY

In 1904 Heller<sup>5</sup> reported the case of a 37 year old man who fell while carrying a heavy burden, with the mass falling on him. Immediately afterward he felt sharp pain in the right breast and in the back. He rested at home for several weeks, suffering from continued pain, dyspnea and fatigue. One month later a systolic murmur was noted over the heart, although its exact location was not recorded. Four months after his accident he was admitted to a hospital because of congestive heart failure with signs of aortic insufficiency, from which he died seven months later. Autopsy disclosed an incomplete tear in the aortic wall just above the valve, resulting in slipping downward of one of the commissures.

In 1922 Gallavardin and Gravier<sup>1</sup> reported the case of a 57 year old baker who had suffered intermittently from dyspnea, edema and ascites for one year before death. There was no record of cardiac pain. The heart was enlarged, and the "classical murmur" of aortic insufficiency was present. The blood pressure was 185 systolic and 50 diastolic. A clinical diagnosis of syphilitic aortic insufficiency was made, although stigmas of syphilis were lacking and the Wassermann reaction was negative. Death was a result of heart failure. At autopsy a gaping healed transverse tear was encountered in the aortic media at the level of the coronary arteries. The authors expressed the belief that the leak was a result of lowering of the affected valve cusps. They were unable to find any cases of a similar condition in the literature but suggested the lesion was frequently overlooked and was not rare.



Gravier<sup>12</sup> demonstrated the truth of the latter observation by reporting a case of a similar occurrence two years later. A 34 year old woman was admitted to a hospital for meningitis. Palpitation and dyspnea on effort had been noted for four years, but there was apparently no history of cardiac pain. There was a diastolic murmur in the third interspace just to the left of the sternum, accompanied by a slight thrill. The pulse was bounding, and Duroziez's sign was positive. At autopsy there was evidence of acute meningitis. In the aorta just above the "posterior" and the "right anterior" valve cusp there was a transverse outpouching of the walls of the vessel about the size of two fingers. Its edges were sharp. A smaller similar rupture was noted just above the left anterior cusp.

Maresch<sup>2</sup> reported 2 additional cases in 1929. A 65 year old street worker was seized in 1920 while working with a sharp pain in the right side of the chest and was unable to work for six weeks. Dyspnea on exertion was noted in 1923, and in January 1924 dull pressure over the heart, pain in the right axilla and severe dyspnea were evident. At this time he was admitted to a hospital because of dyspnea and swelling of the feet. The heart was enlarged; a loud blowing systolic murmur and a soft decrescendo diastolic murmur were heard at the apex. Capillary and arterial pulsations were noted. The blood pressure was not recorded. Death occurred in March 1924 as a result of heart failure. At autopsy two transverse tears were noted in the aortic wall just above the valve. Both were smooth, white and glistening. The valve cusps appeared normal.

The patient in the second case reported by Maresch was a 25 year old man who came to a clinic because of headache and visual disturbances. A diastolic murmur at the aortic area had first been noted during a routine examination two months previously. There was no record of cardiac pain. In the clinic a diastolic murmur was still present. The pulse was bounding. The systolic blood pressure was 204; the diastolic pressure was not given. Death from uremia occurred four months later. At autopsy an old tear 0.5 cm. long with blunt edges and shining white base was noted just above the commissure between the "posterior" and the "right anterior" aortic cusp. The aortic valve was normal.

Lundberg<sup>91</sup> reported 2 interesting cases of incomplete aortic tears in 1930. In the first case the patient was a 68 year old man who had noted dyspnea, edema and "pressure over the chest" for two years. Loud sawing systolic and diastolic murmurs were heard over the aortic

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12. Gravier, L.: Insuffisance aortique fonctionnelle par rupture incomplète de l'aorte, *J. de méd. de Lyon* 5:563, 1924.

area. The blood pressure was 180 systolic and 90 diastolic. The pulse was collapsing, and capillary pulsations were evident. The Wassermann reaction was negative. Death from congestive heart failure resulted. Autopsy disclosed two old healed spiral tears in the walls of the aorta just above the commissures of the aortic valve.

The patient in Lundberg's second case was a 42 year old man who was relatively well until 1923, when

. . . in a state of sexual excitement, the patient suddenly had a feeling that something had burst in his chest. He thought himself that he had burst a blood vessel. At the same time, a loud blowing sound was heard in conjunction with the heart beats to a distance of as much as two meters from the patient's chest.

Five years later he was admitted to a hospital because of dyspnea. The blood pressure was 135 systolic and 55 diastolic, and loud sawing systolic and diastolic murmurs were heard over the whole precordium, with maximum intensity at the aortic area. Other signs of aortic insufficiency were present. Roentgen and fluoroscopic examination showed a broad aortic shadow without local bulging. The Wassermann reaction was 1 plus; it had been 3 plus in 1914 after malaria, but the patient was not thought to have syphilis. Death resulted from heart failure. At autopsy a healed transverse tear was found in the aortic wall just at a commissure of the aortic valve, and there was a smaller tear adjacent to the first one.

Eskelund<sup>13</sup> has apparently reported a case of this condition, but the original reference has not been obtained, and the abstract studied was too brief to permit discussion.

CASE 6.—H. K., a 42 year old Negro, was seized on May 2, 1929 with stabbing pain in the right side of the chest shortly after a heavy meal. The pain was so severe that he could hardly breathe, and he felt as if he were choking. The pain was not related to respirations, and change of position did not relieve it. He had never experienced pain of this sort before. He entered the hospital the following day. Examination of the chest showed no abnormality. The heart was enlarged downward. To and fro murmurs were heard at the aortic area, at the apex and over the vessels of the neck. The pulse was collapsing. The blood pressure was 190 systolic and 40 diastolic. The urine contained albumin (4 plus) and a large number of hyaline casts. The hemoglobin concentration was 75 per cent (Dare). Leukocytes numbered 10,120, and the percentage of polymorphonuclears was 75. Wassermann and Kahn reactions of the blood were negative. The temperature was slightly elevated for several days and gradually returned to normal. The pain subsided in a few days, and the patient was discharged from the hospital several weeks later. The heart murmurs remained unchanged.

Subsequently he was admitted to the hospital nine times because of dyspnea and edema. There was no further cardiac pain. Wassermann and Kahn reactions were

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13. Eskelund, V.: Aortic Insufficiency as Result of Spontaneous Rupture of Aorta, *Ugesk. f. læger* **103**:240, 1941; abstracted, *J. A. M. A.* **117**:814 (Aug. 30) 1941.

repeatedly negative. An electrocardiogram (fig. 6) taken September 21 was interpreted as showing left axis deviation, auricular fibrillation and digitalis effect. The last admission was on Feb. 19, 1930. Examination of the chest showed evidence of fluid in both pleural sacs. There was a diastolic murmur at the aortic area, transmitted to the apex. The pulse was of the Corrigan type. The blood pressure was 150 systolic and 70 diastolic. The abdomen was distended and showed a fluid wave. The scrotum and the lower extremities were markedly edematous. The urine contained albumin (4 plus) and a large number of casts. The hemoglobin concentration was 50 per cent. Leukocytes numbered 9,800, and the percentage of polymorphonuclears was 58. The evidence of congestive heart failure remained, and death occurred February 25, six days after admission.

At autopsy the heart weighed 460 Gm. All the cardiac valves were normal except the aortic valve. There was a tear in the aortic wall just at one of the commissures, and the two affected cusps hung low in the valve ring. The tear was short but gaped widely, and its base was white and hyaline. There was no gross or microscopic evidence of syphilitic aortitis. There was no evidence of medial necrosis in sections taken through the aorta a short distance from the tear. The kidneys were small and firm and showed microscopic evidence of advanced sclerotic changes.

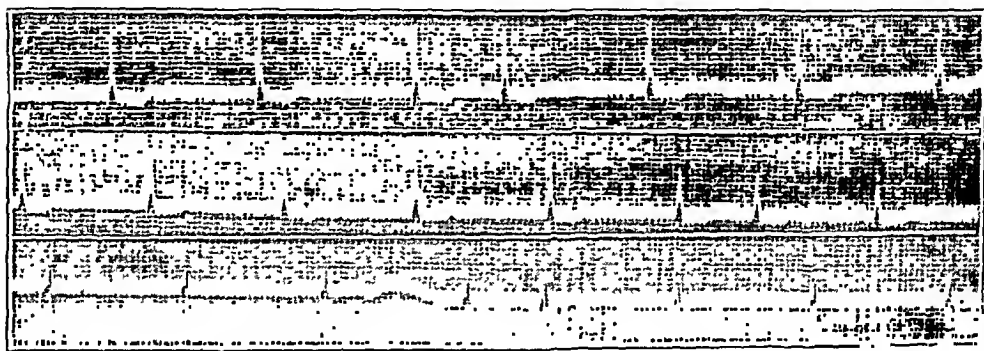


Fig. 6 (case 6).—An electrocardiogram, taken four and one-half months after incomplete rupture of the aorta and five months before death. The tear crossed a commissure of the aortic valve and caused aortic insufficiency. Death was a result of congestive heart failure.

CASE 7.—W. F., a 26 year old Negro, was admitted to the hospital March 4, 1937 because of dyspnea and orthopnea. One month previously pain was noted "under the heart" and was followed by dyspnea, fever and cough. The patient believed he had had "the flu." The character of the pain and the circumstances of its onset were not recorded. On examination the temperature was 96.4 F., the pulse rate 124 per minute, the respiratory rate 40 per minute and the blood pressure 210 systolic and 85 diastolic. There were visible pulsations in the neck. Chest expansion was equal on the two sides, and bilateral basal rales were the only abnormality in the lungs. The apical impulse was in the fifth interspace, 12 cm. to the left of the midline. A palpable thrill was noted over the whole precordium. Systolic and diastolic murmurs were noted both at the mitral and at the aortic area, and the murmurs in the aortic area were transmitted down the left border of the sternum. There was no ascites or edema.

The hemoglobin concentration was 65 per cent (Dare); the red cells numbered 3,800,000, and the white cell count was 7,450, with 73 polymorphonuclears.

Kolmer and Kline reactions of the blood were both negative on two occasions. The urine contained albumin, (3 to 4 plus) and a moderate number of hyaline casts and had a specific gravity of 1.024-1.038. An electrocardiogram (fig. 7) showed marked

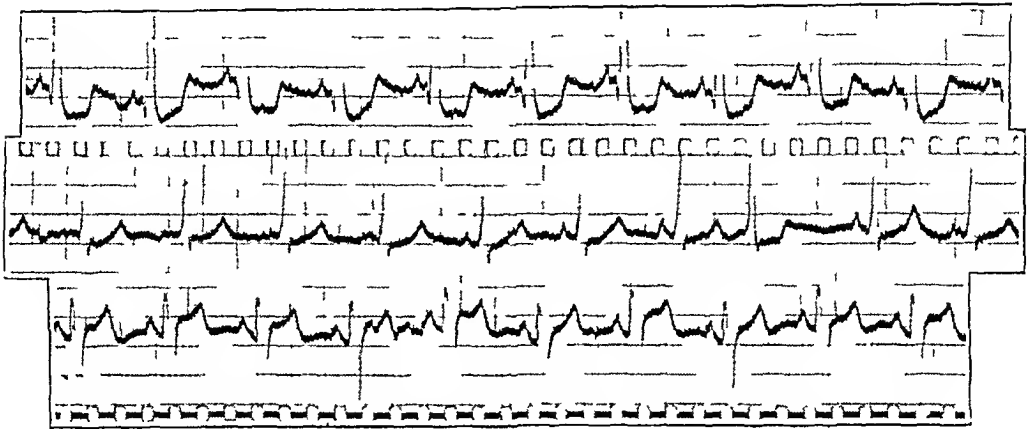


Fig. 7 (case 7).—An electrocardiogram. Two incomplete tears were present in this case. Death occurred about three months after the tears developed and was a result of aortic insufficiency and congestive heart failure.



Fig. 8 (case 7).—A roentgenogram of the chest, taken after the onset of heart failure.

left axis deviation and occasional premature ventricular contractions. The T waves were positive in all leads. A roentgenogram of the chest (fig. 8) showed evidence of hypertrophy of the left ventricle and congestion of the pulmonary fields.

Pain in the chest and dyspnea persisted in spite of administration of digitalis and sedatives. No changes in the heart sounds were noted. The blood pressure remained elevated, the lowest recorded pressure being 180 systolic and 80 diastolic. Generalized anasarca developed, and death occurred from congestive heart failure seven weeks after admission, probably three months after the time of the original tear.

At autopsy there was a moderate amount of fluid in the serous sacs. The heart weighed 450 Gm., and the myocardium of the left ventricle was moderately hypertrophied. The mitral, the tricuspid and the pulmonary valve appeared normal. The cusps of the aortic valve were normal, but they were separated from the aortic wall by transverse tears across two of the commissures (fig. 9). The obvious effect was

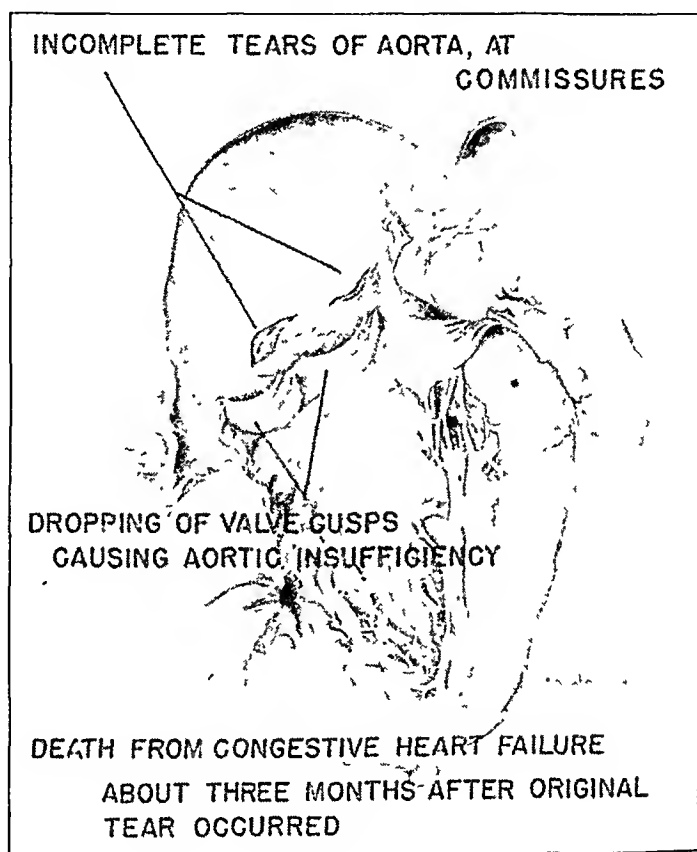


Fig. 9 (case 7).—Artist's drawing of the autopsy specimen. The blood pressure in this 26 year old Negro was 210 systolic and 85 diastolic. The symptoms at the time the tears probably occurred were vague; the patient thought he had "the flu."

to prevent normal approximation of the three cusps during diastole, permitting aortic regurgitation.

There was no grossly evident disease of the aorta at the site of the tears or elsewhere. The tears were transverse, and the longer one was 1 cm. in length and gaped about 5 mm. Near one end of one of the slits there was some bridging of the defect by remnants of media covered over by endothelium. There was no evidence of thrombosis. Microscopic sections taken across the tear showed degeneration of the muscle and the elastic tissue of the media and replacement by a mucoid sort of fibrous tissue. A few mononuclear cells were evident in the base of the tear, but the

vasa vasorum appeared normal. Sections of the aorta taken a few centimeters away from the tears did not show any recognizable abnormality.

Other findings at autopsy consisted of gross and microscopic evidence of arteriolar nephrosclerosis, as well as relatively recent lobar pneumonia affecting the lower lobe of the right lung.

(See also case 11).

In cases 6, 7 and 11 the clinical signs of aortic insufficiency were present, and in 7 of the 9 cases in this group death resulted from congestive heart failure. Yet in none of the 7 cases were the cusps of the aortic valve rolled, thickened, shortened or otherwise abnormal.<sup>14</sup>

Garvin<sup>15</sup> has reported 14 instances in which diastolic murmurs were heard at the aortic area in cases of severe hypertension. In all of these cases the aortic valve appeared normal at autopsy, and the murmurs were considered functional. No description of the aortas was given. Possibly in some of these cases there were inconspicuous aortic tears; many incomplete tears are not recognized on casual examination.

#### DISSECTING ANEURYSM PROBABLY FOLLOWING INCOMPLETE TEAR

It is difficult to pick out of the extensive literature on dissecting aneurysm cases in which dissection has occurred in stages. Cases probably representing this process have been reported by Letulle,<sup>9b</sup> Uhles,<sup>9c</sup> Klotz and Simpson,<sup>9j</sup> Hamman and Apperly<sup>9i</sup> and Roberts.<sup>9n</sup>

CASE 8.—J. T., a 45 year old Negro who was previously in good health, was suddenly seized on Nov. 13, 1936 with sharp, knifelike pain between the shoulder blades and in the middle of the chest anteriorly. The pain came on while the patient was walking along the street and was accompanied by a choking sensation, dizziness and weakness. The pain remained severe for about five minutes and then gradually lessened, although it did not disappear. On the following day a similar attack occurred, followed this time by orthopnea. He was admitted to the hospital on November 15. On examination the temperature was 101.4 F., the pulse rate 108 per minute, the respiratory rate 22 per minute and blood pressure 130 systolic and 60 diastolic. Slight bulging was noted in the third and the fourth interspace just to the left of the sternum, and there was a thrill in this area. Systolic and diastolic murmurs were noted in the aortic area. There was no tracheal tug. There were numerous moist rales in the bases of both lungs. The remainder of the examination revealed nothing abnormal. There was no edema or ascites. Examination of the blood showed a hemoglobin concentration of 55 per cent, a red cell count of 2,950,000 and a white cell count of 15,000, with 56 per cent granulocytes, of which 11 per cent were band forms. The Kahn reaction of the blood was 4 plus. Two days after admission, the

14. A similar situation doubtless prevails when the mouth of an aneurysm, either syphilitic or mycotic, is located just above one of the commissures of the aortic valve. Two cases of such a condition, in which there were clinical signs of aortic insufficiency, are represented by specimens preserved in the pathology museum of the George Washington University School of Medicine.

15. Garvin, C. F.: Functional Aortic Insufficiency, *Ann. Int. Med.* **13**:1799, 1940.

temperature was normal, the pulse rate 74 per minute and the blood pressure 120 systolic and 65 diastolic. Systolic and diastolic murmurs were still evident at the aortic area. On that day the patient got out of bed against instructions. About one hour after being put back to bed he suddenly cried out that he was choking. When he was seen by the intern a few minutes later the blood pressure was 60 systolic and 40 diastolic and he was in shock. He died a few hours later, without any apparent change in his condition.

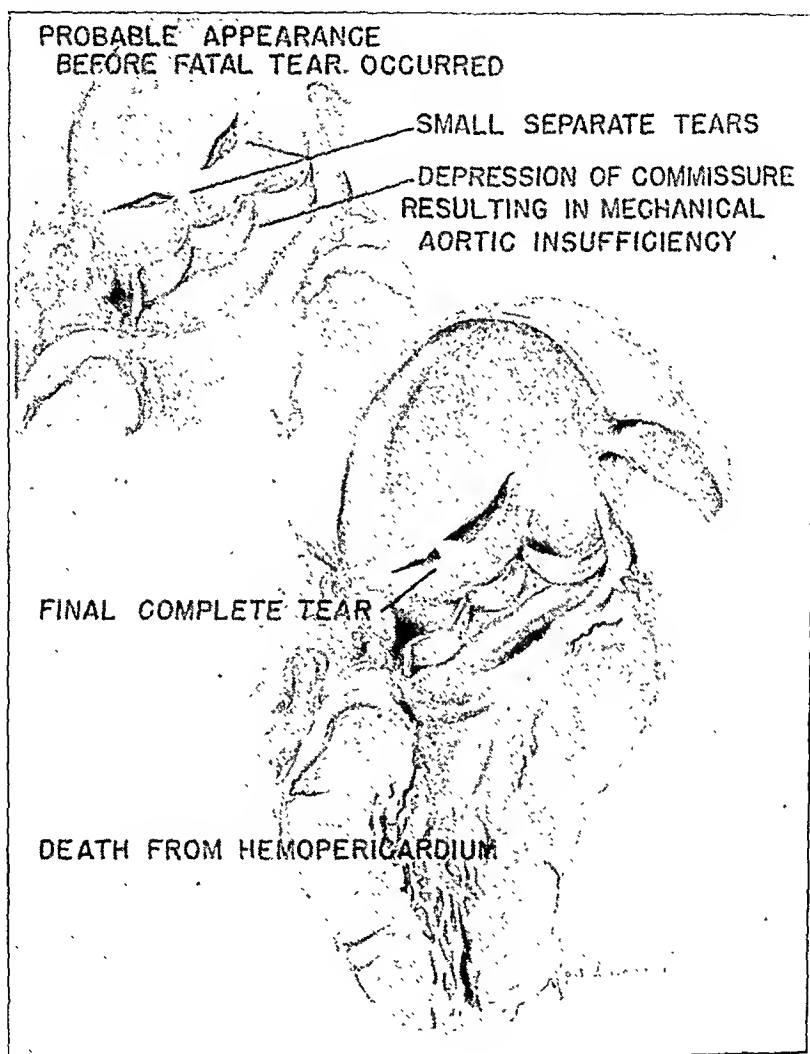


Fig. 10 (case 8).—Artist's drawing from the necropsy specimen. The inset shows the probable appearance of the lesion before the final complete rupture occurred.

At autopsy the pericardium was found to be tense with clotted blood. About 1 cm. above the aortic valve was a large transverse rent (fig. 10) in the wall of the aorta which almost completely encircled it. This rent appeared to consist of two separate tears in line with each other, which subsequently joined when complete rupture occurred. A short dissection extended proximally and ruptured into the pericardial sac, involving a total distance of approximately 2 cm. There was no evidence of syphilitic aortitis or of medial necrosis, either grossly or microscopically.

This case is believed to represent partial rupture of four days' duration, with complete rupture occurring on the fourth day through the base of the older tear.

CASE 9.—L. W., a Negress, was first seen in the dispensary on Oct. 13, 1931, when she was 30 years old. Her sixth pregnancy had been interrupted nineteen months previously because of toxemia and hypertension. In the dispensary the blood

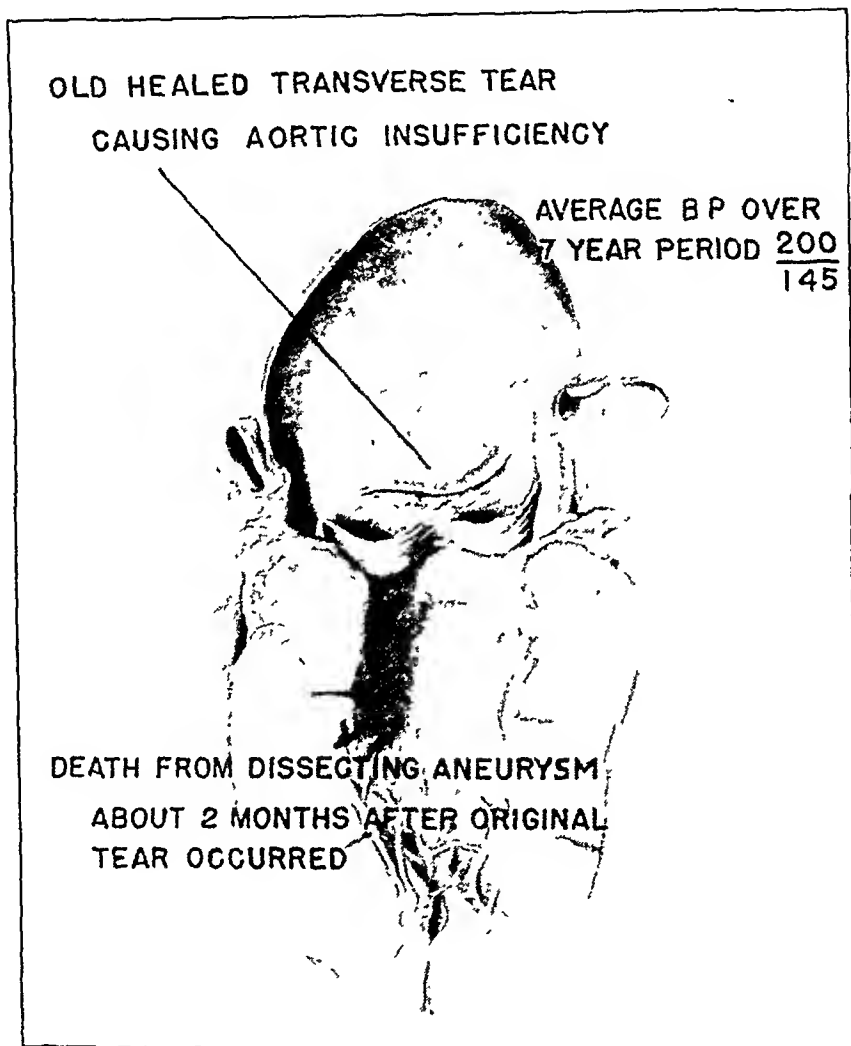


Fig. 11 (case 9).—Artist's drawing of the autopsy specimen. Two other tears were present in the aortic wall but could not be shown in the drawing. The short dissection into the pericardium which caused death occurred through the base of the tear shown.

pressure was 210 systolic and 140 diastolic. The heart was found to be slightly enlarged, but no murmurs were heard. From this time until September 1935 she was under regular observation in the clinic, complaining of headache, insomnia and dyspnea on exertion. There was no precordial pain, and at no time were murmurs heard. The average of thirty-seven determinations of blood pressure during this period was 217 systolic and 134 diastolic. In September 1935 she was admitted to the hospital because of precordial pain, dyspnea and edema of the ankles. The blood pressure was 260 systolic and 160 diastolic. A rasping systolic murmur was noted



over the aortic area. The Kahn reaction of the blood was negative. The results of other laboratory examinations were not remarkable. She was discharged from the hospital two weeks later, free from pain. From this time until February 1937 she was seen regularly in the dispensary and was readmitted to the hospital several times because of dyspnea and severe headaches. The average blood pressure during this period was 238 systolic and 146 diastolic. On February 9 a rough, rasping, diastolic murmur was noted in the aortic area. This change in the character of the murmurs caused a diagnosis of subacute bacterial endocarditis to be considered. Presumably there was no precordial pain at this time. Both the systolic and the diastolic murmur persisted for at least a month, although the blood pressure remained unchanged (an average of 248 systolic and 149 diastolic). On April 5 she was readmitted to the hospital because of dyspnea, retrosternal pain and swelling of the ankles. The blood pressure was 240 systolic and 170 diastolic. The apical impulse was in the sixth interspace 13 cm. to the left of the midline. There was a loud systolic murmur heard best in the fourth interspace just to the right of the sternum, but no diastolic murmur was noted. The Kahn reaction was again negative. Roentgen examination of the chest showed great enlargement of the heart and fusiform dilatation of the aorta. Two days after admission the patient had an attack of severe dyspnea and died in a few minutes, without mention of pain.

At autopsy the kidneys were small and contracted and showed microscopic evidence of arteriolar sclerosis. The pericardial sac was greatly distended with blood. On opening of the aorta there was a healed transverse tear 2 cm. long just above the posterior commissure of the aortic valve and crossing the two adjacent cusps (fig. 11). This tear gaped widely and communicated with a short dissecting channel through which rupture into the pericardial sac occurred. Two old healed tears were apparent in the ascending aorta, although somewhat higher up. One of these was longitudinal, the other oblique. There was no gross or microscopic evidence of syphilitic aortitis or of medial necrosis (fig. 2).

In this case there had obviously been two healed incomplete ruptures of the aorta and probably a third. One of the higher incomplete tears probably occurred in September 1935, seventeen months before death. At this time a rasping systolic murmur was first noted over the aortic area, and the patient complained of precordial pain. The finding of a diastolic aortic murmur two months before death suggests that an incomplete transverse tear just above the aortic valve occurred at that time and that the final complete rupture occurred through its base. It does not appear likely that either of the healed tears above this level could have caused a diastolic murmur.

CASE 10.—F. W., a 47 year old Negro, had a "choking spell" on Feb. 19, 1939 while eating dinner. This was followed immediately by substernal pain, dyspnea and cough. On admission to the hospital two days later he was complaining of dyspnea and of pain in both sides of the chest and in the back, made worse by inspiration. Two years previously he had been thought to have tuberculosis. On examination the temperature was 99 F., the pulse rate 100 per minute, the respiratory rate 22 per minute and the blood pressure 195 systolic and 130 diastolic. The head and neck were normal. The apical impulse was noted in the fifth left interspace in the nipple line, and the heart was not thought to be enlarged. The rhythm was regular, and there were no murmurs or thrills. The lungs showed slight impairment of percussion note and a few fine rales over the apexes posteriorly. The remainder of the examination showed nothing essentially abnormal. The urine

was normal. The blood urea nitrogen was 15 mg. per hundred cubic centimeters. The Kahn reaction of the blood was negative. A roentgenogram of the chest, taken three days after admission, showed scattered areas of increased density in the upper lobe of the right lung, which were thought to represent areas of tuberculosis. The heart was enlarged in its transverse diameter, and the aorta was moderately widened. Examinations of sputum were negative for tubercle bacilli.

The temperature rose to 101 F. a few hours after admission and subsequently fell gradually to normal. Pain disappeared in a few days, but cough persisted. The pulse rate varied from 100 to 134 per minute. On February 27 the patient attempted to get out of bed but suddenly collapsed and was dead in a few moments.

At autopsy there were a few calcified old tuberculous lesions in the upper lobe of the right lung, without evidence of recent activity and without pleural involvement. The pericardial sac contained about 500 cc. of clotted blood. At the orifice of the left coronary artery there was a short transverse tear in the aortic wall, reaching to each of the adjacent valve commissures but not crossing them. The tear gaped slightly, and there was a short dissection in its base along the course of the coronary artery. About 2 cm. from the beginning of the dissection there was a hematoma in the epicardium, through which rupture occurred into the pericardial sac. There was no evidence of syphilitic aortitis, and no medial necrosis was apparent.

It is believed that a small incomplete rupture of the aorta occurred on February 19 and that eight days later, as the patient was climbing out of bed, a tear occurred through the base of the old lesion, resulting in dissection and almost immediate death from cardiac tamponade.

CASE 11.—E. B., a 64 year old Negro, was suddenly seized with sharp pain in the right side of the chest on April 20, 1939. Previously he had thought he was completely well. The pain was made worse by movements of the body and by inspiration. He became short of breath immediately after the onset; he had never been dyspneic before. Slight cough developed, and on three occasions the sputum was blood tinged. Pain and dyspnea became worse, and he was admitted to the hospital on April 24.

On examination the temperature was 99.8 F., the pulse rate 118 per minute, the respiratory rate 26 per minute and the blood pressure 140 systolic and 80 diastolic. The head and neck were normal. There was slight lag of the right side of the chest on respiration. Dulness and many fine and coarse rales were noted at the base of the right lung posteriorly. The heart was enlarged, the apical impulse being in the sixth interspace 15 cm. to the left of the midsternal line. Numerous premature contractions were noted. There was a harsh systolic murmur at the apex, thought to be of crescendo type. The remainder of the examination revealed nothing abnormal. There was no edema.

The urine contained hyaline and granular casts but was not otherwise abnormal. The Kahn reaction of the blood was negative. Roentgen examination of the chest showed mottled areas of increased density in the lower half of the right pulmonary field. The heart was markedly enlarged in its transverse diameter, and the aorta was widened. On the first examination the sputum was reported positive for tubercle bacilli, but on ten subsequent examinations none was found. The hemoglobin concentration was 53 per cent; the red cells numbered 3,300,000, and the white cell count was 11,700. Eighty-nine per cent of the leukocytes were neutrophils, including 28 per cent band forms. The Kahn reaction of the blood was negative.

Pain and dyspnea disappeared after two days' rest in bed. The temperature was 99-101.6 F. for the first week and ranged between 99 and 100 F. for the second week; thereafter it was normal throughout the patient's stay in the hospital. The pulse rate was 100-120 per minute for the first five days and thereafter was usually 70 to 90 per minute. On May 9—after the temperature had been normal for several days—roentgen examination of the chest showed no change in the density in the right lung. On May 16, the blood pressure was 185 systolic and 100 diastolic and the heart action was irregular. On May 26, bronchoscopy revealed lack of respiratory movement of the right main bronchus but no tumor or other abnormality was noted. The patient was kept under observation until June 1, when he was discharged as cured. The final diagnosis was bronchopneumonia.

The patient was readmitted on September 12 because of dyspnea, edema of the ankles and weakness. There had been no further pain in the chest. The temperature

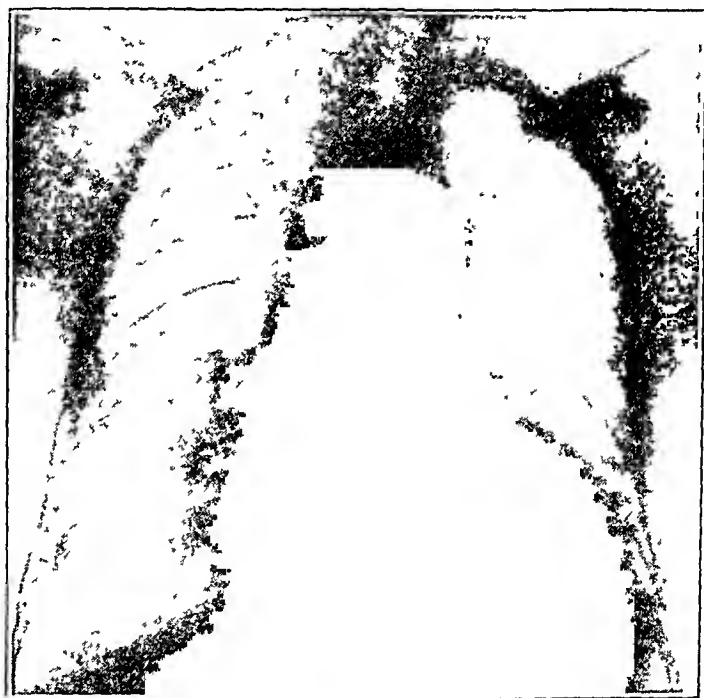


Fig. 12 (case 11).—A roentgenogram of the chest, taken five months after incomplete aortic tear probably occurred. The patient was in congestive failure due to aortic insufficiency.

was 98 F., the pulse rate 88 per minute, the respiratory rate 28 per minute and the blood pressure 148 systolic and 94 diastolic. The veins of the neck were distended and there were marked pulsations in the arteries and veins. There was moderate dulness over the bases of both lungs posteriorly, and numerous rales were noted. The heart was enlarged, the apical impulse being in the sixth interspace in the axillary line on the left side. A hollow, blowing diastolic murmur was heard at the aortic area and transmitted downward along the left side of the sternum. A short, rough, systolic murmur was also noted at the aortic area. Both could be heard over the apex. There were frequent extrasystoles. The liver was palpably enlarged and tender. There was marked edema of the legs.

The hemoglobin concentration was 80 per cent; the red cell count was 3,800,000, and the leukocytes numbered 4,400. The differential count was normal. The urine

contained a faint trace of albumin and a moderate number of leukocytes. The blood urea nitrogen was 15 mg. per hundred cubic centimeters. The Kahn reaction was negative. The result of the phenolsulfonphthalein test showed 17.5 per cent elimination of the dye in the first hour and 20 per cent in the second hour. On ten examinations the sputum was negative for tubercle bacilli. Roentgen examination of the chest (fig. 12) on October 3 showed persistent mottled density extending outward from the right hilar area. The heart was enlarged downward and to the left, and the aortic area was widened. An electrocardiogram (fig. 13) taken September 18 showed marked left axis deviation.

The temperature was normal throughout the patient's stay in the hospital. The pulse rate varied from 80 to 130 per minute. The respiratory rate was slightly increased throughout his stay. On October 1 dyspnea and edema were still present

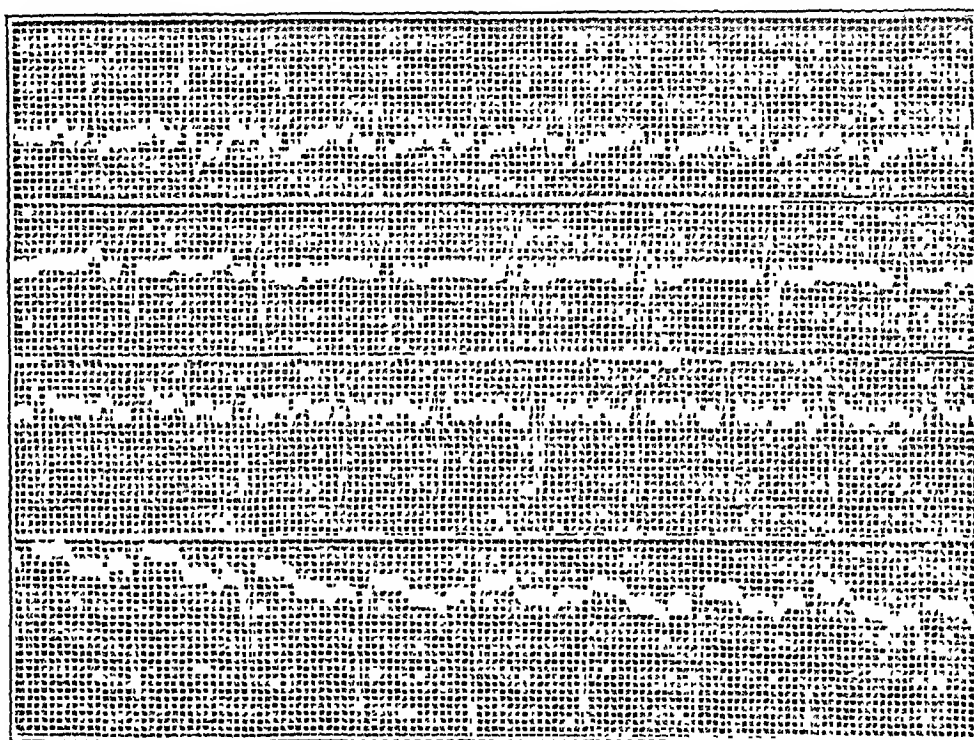


Fig. 13 (case 11).—An electrocardiogram, taken five months after the original tear probably occurred, two months before death. At the time this tracing was taken the patient was in congestive heart failure due to aortic insufficiency.

in spite of digitalis therapy. One week later edema had disappeared, but dyspnea was still present. The blood pressure was 160 systolic and 110 diastolic. Improvement continued, although the heart murmurs persisted unchanged. Arrangements were being made for his transfer to a convalescent home. On November 19 he was found dead, sitting in a chair with his head on the bed. He had died suddenly, without an outcry.

At autopsy the heart was found to be enlarged, weighing 800 Gm. The left ventricle was greatly hypertrophied. The pericardial sac was distended with partially clotted blood. All the cardiac valves appeared completely normal. There was a large gaping rent in the walls of the right side of the aorta shaped like a reversed letter C (fig. 14). The lower limb crossed just above the commissure between the anterior and the right posterior cusp of the aortic valve. This portion of the tear did not penetrate the aorta and appeared to be older than the remainder.

The upright limb and the upper transverse limb of the tear extended through the full thickness of the walls and led directly into the pericardial sac. Sections showed no evidence of syphilitic aortitis or of medial necrosis.

In this case the original incomplete tear probably occurred seven months before death, and as the tear gaped the aortic valve sagged and

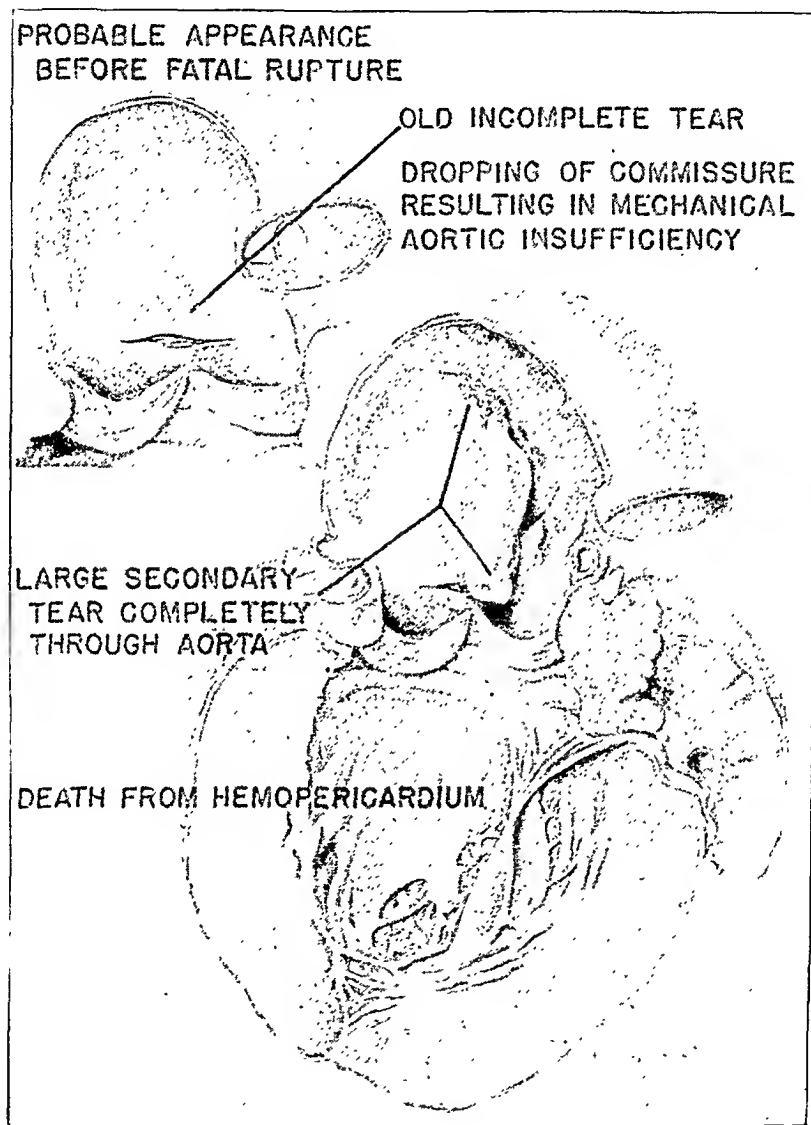


Fig. 14 (case 11).—Artist's drawing of the necropsy specimen. The inset shows the probable appearance of the aorta after an incomplete tear occurred, causing aortic insufficiency. Seven months later the tear extended, causing sudden death from hemopericardium and cardiac tamponade.

valvular insufficiency resulted. Undoubtedly the congestive heart failure on the second admission was due to aortic insufficiency. Subsequently, complete tear and dissection tended to obliterate the evidence of the old incomplete tear.

## SUMMARY

Incomplete rupture of the aorta is closely akin to dissecting aneurysm; it is the condition which exists after a tear has occurred in the vessel wall but before dissection has begun. It may, in the absence of dissection, cause pain in the chest and sudden dyspnea and is frequently associated with murmurs at the aortic area of the precordium. It is probably more frequent than dissecting aneurysm proper and may or may not be followed by dissecting aneurysm. If incomplete tear was recognized clinically dissection might be prevented in some cases by measures which tend to lower the blood pressure, thus permitting healing of the vessel wall.

The following suggestions may be of help in making an antemortem diagnosis of incomplete rupture of the aorta:

If a patient has been under observation for hypertension and returns complaining of sudden suffocation and dyspnea, with or without substernal pain, and if examination discloses either a systolic or a diastolic aortic murmur or both—murmurs which had not been present previously—incomplete aortic rupture should be strongly suspected. A harsh or rasping type of murmur would be particularly suggestive.

If the patient is seen for the first time during an acute attack, the diagnosis of incomplete rupture of the aorta would have to be made largely by exclusion. If no murmurs are detected, an incorrect diagnosis of coronary thrombosis may be made. If there is a diastolic murmur at the aortic area, a diagnosis of syphilitic aortic valvulitis may be made, and the pain and suffocation may be assigned to narrowing of the coronary ostiums. The coincidence of hypertension and negative serologic reactions for syphilis may raise some doubt as to the correctness of this diagnosis. The suddenness of onset of symptoms may cause the diagnosis of ruptured aortic valve cusp to be considered. In dissecting aneurysm, which might also be confused with incomplete rupture, pain is usually more severe, and characteristically, the severity and the location of the pain change as dissection continues.

If the patient is seen for the first time because of heart failure due to aortic insufficiency, the correct diagnosis of incomplete aortic rupture would be extremely difficult. If the onset of symptoms of heart failure is sudden, if the patient shows marked hypertension and if clinical evidence of syphilitic and of rheumatic infection is lacking, it may occasionally be possible to make a correct diagnosis of incomplete aortic rupture as the cause of aortic insufficiency.

Careful search of the literature has failed to disclose an instance in which a correct diagnosis of incomplete rupture of the aorta has been made ante mortem.

# CONTROL BY RADIUM FOR GASTRIC ACIDITY

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The importance of hyperacidity of the gastric juice as a factor in the causation of duodenal ulcer and of chronic dyspeptic symptoms is widely recognized. Most forms of treatment aim at controlling hyperacidity by means of repeated chemical neutralization or by surgical intervention. The occurrence of gastrojejunal ulceration following surgical treatment, however, suggested that other methods for the control of gastric acidity might be tried, and to this end a study was made of the effects of irradiation of the gastric mucosa by radium.

## METHOD

As a preliminary 3 elderly patients with a long history of duodenal ulceration were selected for trial, and later, as the results were promising, a number of younger patients with hyperacidity and a shorter history also underwent treatment. In all cases gastric function was studied before and after the use of radium. Either two 25 mg. needles or four 10 mg. needles of radium were secured in the end of a stout rubber tube, which was swallowed like a Ryle tube. The end of the tube containing the radium needles was surrounded by a rubber bag, which was distended with water when in position in the stomach. This arrangement prevented the needles from passing on into the duodenum and also held them off the stomach wall. Position was controlled by roentgen examination, and treatment was carried out in four to five hour periods daily until a total dose of 2,000 to 2,500 milligram-hours had been administered.

To determine the secretory activity of the gastric mucosa some form of gastric analysis is essential. The test usually employed is the fractional test meal of gruel, which gives a rough quantitative measure of the concentration of acid in the gastric juice. Early specimens, however, are much diluted by the gruel of the meal, while the extent of the dilution in later specimens depends on the rate of emptying of the stomach. Only when all the meal has passed through the pylorus is relatively pure gastric juice obtained. Gruel also does not constitute a maximum stimulus for gastric secretion, as is shown by the fact that while the first test meal to which a patient is subjected may suggest the presence of achlorhydria, in subsequent tests a normal acid secretion may result. Furthermore, with gruel meals no information regarding the volume of juice secreted is obtained.

In order to secure data on the secretory capacity of the gastric mucosa, we studied the concentration of acid and the rate of gastric secretion after the subcutaneous injection of histamine acid phosphate using the technic of Bloomfield and

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Polland<sup>1</sup> and Polland<sup>2</sup> with certain minor variations suggested by Lander and Maclagan.<sup>3</sup> Study of the gastric secretion following administration of histamine acid phosphate has the following advantages: The procedure is standardizable; it provides a maximum stimulus to secretion, and it yields pure gastric juice suitable for volume measurement and for chemical analysis.

Tests were carried out at 9 a. m., no food or fluids having been taken by the subject since the previous evening. A Ryle tube was passed, the resting juice aspirated and the stomach then washed out with several syringefuls of water. This acts as a lavage to remove mucus and is also an indication of the satisfactory placing of the tube, since with the bulb in the most dependent portion of the stomach a syringeful of water passed into the empty stomach should be recoverable in approximately equal volume. One milligram of histamine acid phosphate was then given subcutaneously, and more or less continuous aspiration of the gastric juice was employed throughout the subsequent fifty minutes, the juice being saved in ten minute specimens in separate bottles. Free acidity was then determined by titration with sodium hydroxide solution, with Töpfer's reagent (0.5 per cent alcoholic solution of dimethylaminoazobenzene) used as an indicator, while the rate of secretion per hour of gastric juice was calculated from the volume of juice collected in the forty minute period between ten and fifty minutes after injection of histamine. By adding together the amounts of tenth-normal free hydrochloric acid in each of these four specimens and multiplying this total by 1.5, the rate of secretion per hour expressed in terms of cubic centimeters of tenth-normal hydrochloric acid was determined.

#### RESULTS

Treatment with radium was employed in 14 cases of duodenal ulcer. In 1 case the effects on the gastric secretion were assessed by means of the gruel meal only, in 10 by histamine tests only and in 3 both by gruel meals and by histamine tests. In all, thirty tests of gastric function were carried out prior to radium treatment and forty-four after treatment.

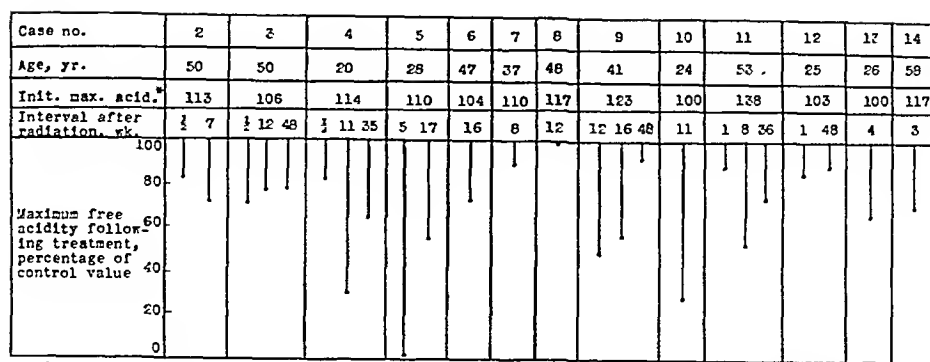
*Response of Gastric Function to Histamine.*—These tests were carried out according to the technic just described. In 10 cases more than one control test was done prior to irradiation, and in each instance there was remarkably close agreement between the first and subsequent tests, a fact which confirms Polland's view that histamine produces the maximum response of which the stomach is capable. The results of these investigations conducted before and after treatment with radium are considered under three main headings: (1) maximum free acidity in the samples of gastric juice (fig. 1), (2) rate of secretion of gastric juice per hour (fig. 2) and (3) rate of secretion of tenth-normal hydrochloric acid per hour (fig. 3). The results are set out diagrammatically according to a uniform plan. In each figure the line marked "100" represents for each case the control, or initial, level of the factor under

1. Bloomfield, A. L., and Polland, W. S.: The Diagnostic Value of Studies of Gastric Secretion, *J. A. M. A.* **92**:1508 (May 4) 1929.

2. Polland, W. S.: Histamine Test Meals, *Arch. Int. Med.* **51**:903 (June) 1933.

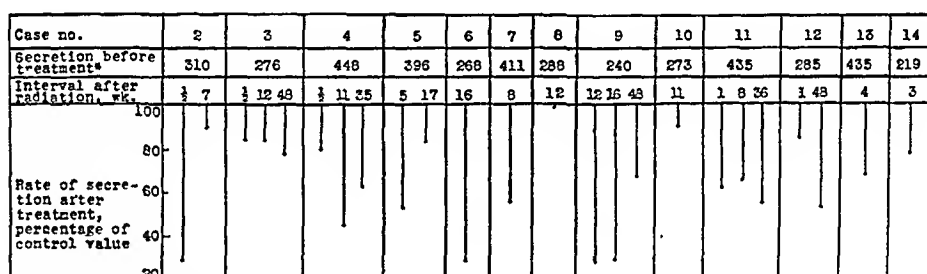
3. Lander, F. P. L., and Maclagan, N. F.: One Hundred Histamine Test Meals on Normal Students, *Lancet* **2**:1210 (Dec. 1) 1934.





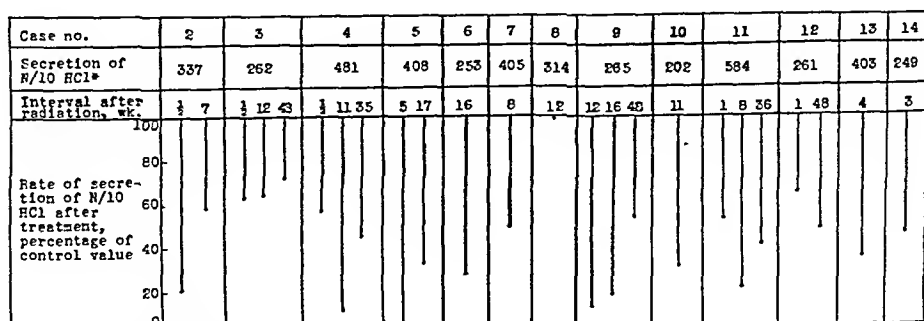
\*Cubic centimeters of tenth-normal hydrochloric acid per hundred cubic centimeters of gastric juice.

Fig. 1.—Maximum free acidity before and after treatment with radium. The length of a line represents the percentage fall in maximum free acidity following treatment, while the dot at the foot represents this factor following treatment expressed as a percentage of the maximum free acidity before treatment.



\*Cubic centimeters per hour.

Fig. 2.—Rate of secretion of gastric juice before and after treatment with radium. The length of the line represents the percentage fall in the rate of secretion of gastric juice following treatment, while the dot at the foot represents the rate following treatment expressed as a percentage of the rate before treatment.



\*Cubic centimeters per hour.

Fig. 3.—Rate of secretion of tenth-normal hydrochloric acid in the gastric juice before and after treatment with radium. The length of the line represents the percentage fall in the rate of secretion following treatment, while the dot at the foot represents the rate following treatment expressed as a percentage of the rate before treatment.

consideration prior to irradiation with radium, while the vertical line drawn downward from this level indicates the percentage of the original value to which this factor has been reduced as the result of treatment. Thus, in a given test a reduction of maximum free acidity to 0 per cent means that all specimens of gastric juice obtained were achlorhydric.

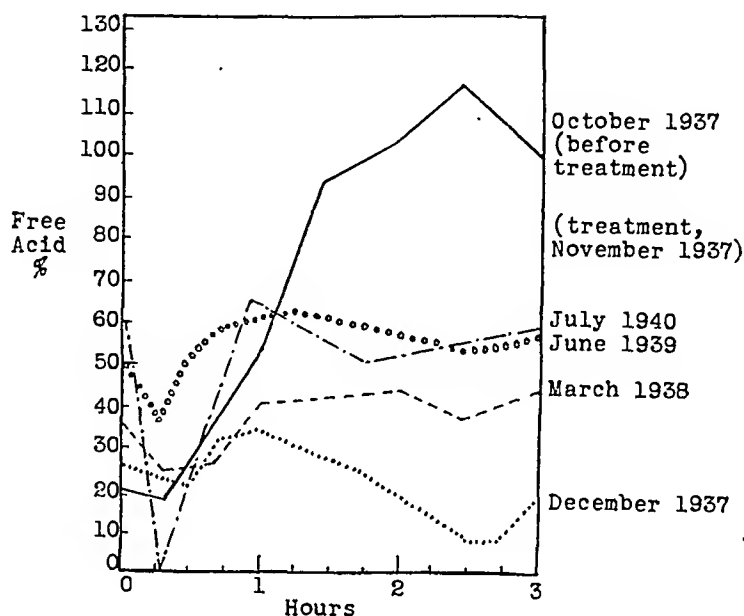


Fig. 4 (case 1).—Gastric function before and after treatment with radium, as measured by the response to a gruel test meal.

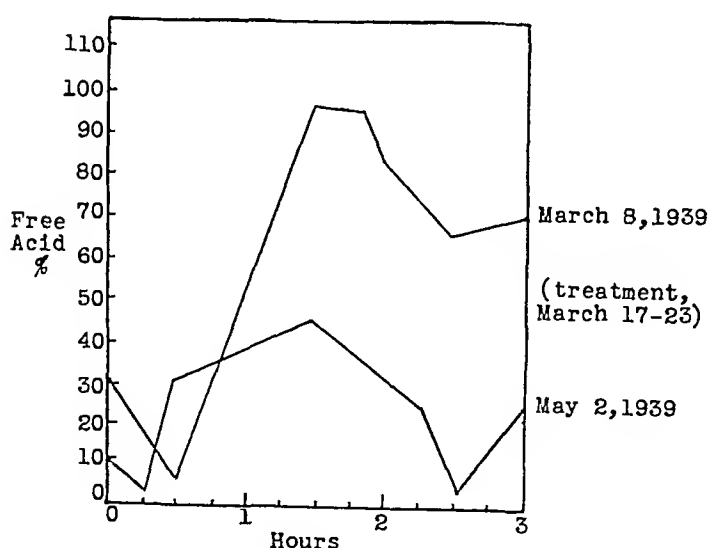


Fig. 5 (case 2).—Gastric function before and after treatment with radium, as measured by the response to a gruel test meal.

*Response of Gastric Function to Gruel.*—In 3 cases (2, 3 and 4) both histamine and gruel tests were employed, while in 1 (case 1) the gruel meal alone was used.

CASE 1 (fig. 4).—This patient was the first to undergo radium treatment, which was commenced in November 1937. The control test showed delay in emptying the stomach, with food and starch still present at the end of three hours, and a high, climbing curve which reached a maximum free acidity of 110 per cent. Numerous tests have been done since, and in all there is a significant reduction in free acidity.

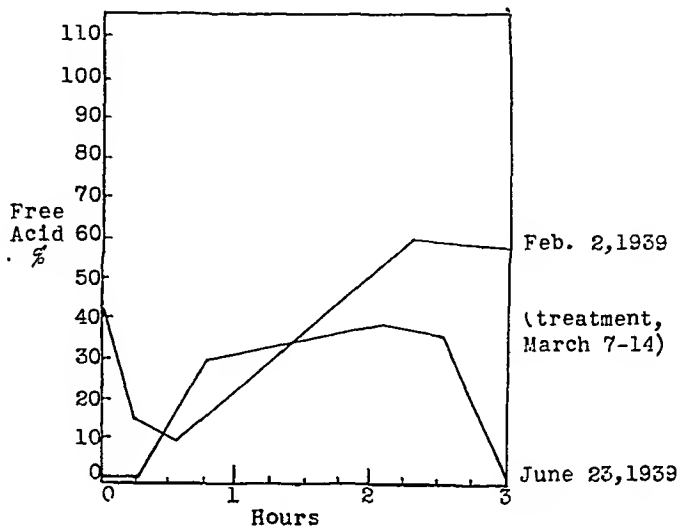


Fig. 6 (case 3).—Gastric function before and after treatment with radium, as measured by the response to a gruel test meal.

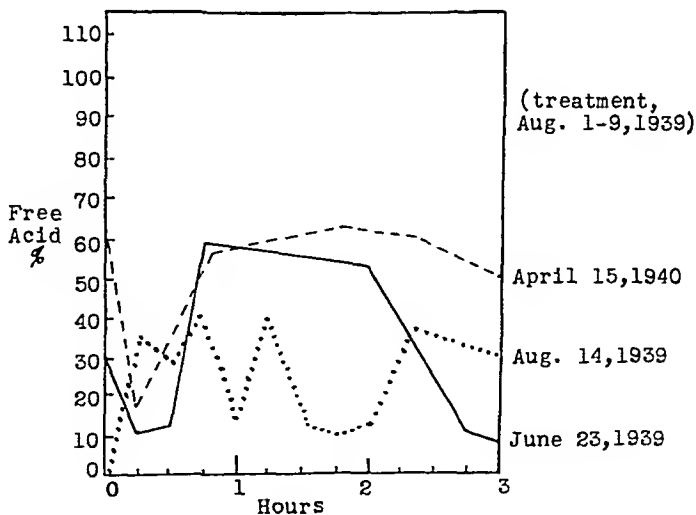


Fig. 7 (case 4).—Gastric function before and after treatment with radium, as measured by the response to a gruel test meal.

CASE 2 (fig. 5).—Seven weeks after treatment the maximum free acidity was approximately half that in the control test, while the acidity of the juice during rest and of the juice remaining at the end of the test was also markedly reduced.

CASE 3 (fig. 6).—Fifteen weeks after treatment the climbing curve typical of duodenal ulcer was replaced by a curve at a lower level, with no free acid in the juice obtained during rest or at the end of the test.

CASE 4 (fig. 7).—Nine weeks after treatment the concentration of free acid was lower than in the control test. The emptying time of the stomach, however, was one and a quarter hours, in place of two and three-quarters hours, so that dilution with food ceased much earlier and consequently the actual acid secretion following treatment was less than would appear from a simple comparison of the acid curves alone. Eight months later the curve had returned to a level slightly higher than the original one.

#### COMMENT

The aim of this investigation was the treatment of hyperacidity causing chronic symptoms. In most cases, if not in all, duodenal ulceration was present: In all 14 the patients presented symptoms typical of this condition; in 10 the presence of an ulcer was proved by roentgen examination; perforation had occurred in 1, while in 3 others there was an initial strongly positive reaction for occult blood in the feces, which later became negative as the result of medical treatment. Reduction in gastric acidity following irradiation was encountered in 13 of 14 cases and was of an order which was not likely to be fortuitous. In the remaining case (8) there was no change, and no attempt was made to secure an effect by increasing the dose. In the histamine series both the concentration of free acid and the rate of secretion of juice were reduced, while the rate of secretion of tenth-normal hydrochloric acid per hour, depending on both these factors, showed in every case a greater reduction than did either separately. Of the 13 cases in which a decrease was obtained, the patient in 1 has been followed up for two and a half years, and those in 3 for one year, in 2 for over eight months and in all except 2 of the remainder for over four months. Sufficient time has not yet elapsed to warrant a definite statement regarding the permanence of this fall in acidity. There is some indication, however, that gastric acidity does not remain at the lowest level indefinitely but that it gradually rises again toward a more normal level (figs. 3 and 4).

No ill effects, either immediate or delayed, were encountered in any case, and in particular repeated examinations of the blood failed to show evidence of any interference with the hematopoietic system.

In considering the clinical results associated with these 13 cases in which reduction of acidity was obtained, we found that in 7 cases (4, 5, 9, 10, 11, 12 and 13) the patients became free of symptoms in the absence of further alkali treatment. Four in particular put on weight and commented on a sense of well-being during the subsequent months. These 7 were the youngest patients in the series, and their symptoms

had been of comparatively short duration. They were, therefore, the most promising subjects for treatment. In 5 other cases (1, 3, 6, 7 and 14) the patients stated that there was definite improvement, with reduction in the severity and frequency of symptoms, but that complete freedom had not been obtained. Intermittent treatment with alkalis had been necessary, but possibly in some instances as a precautionary measure. These patients were older than those in the previous group, and their symptoms had been of many years' duration.

In the remaining case (2) the patient, although the chemical results were satisfactory, was not improved clinically and was operated on seven weeks after radium treatment, when it was found that the ulcer had penetrated into the pancreas, thus explaining the failure to improve, either with alkali therapy before irradiation or after radium treatment. The pathologic report on the specimen of gastric mucosa removed after irradiation was as follows:

The mucosa has an atrophic appearance with a striking absence of rugae, especially in the body and in the pyloric region, the whole mucosa appearing even, smooth, velvety and thinner than normal. A section taken 1 inch (2.5 cm.) up the greater curvature away from the pyloric segment and corresponding to the area of atrophy seen by the naked eye shows typical fundus glands. Approximately the middle third of the length of the glands is occupied almost entirely by oxyntic cells, which present a normal appearance. Further sections at intervals of an inch up the greater curvature to the fundus contain a similar proportion of healthy oxyntic cells. The mucosa shows a marked infiltration with plasma cells, and there is no apparent effect of the irradiation on the blood vessels.

It is, of course, impossible to state how much of this appearance was due to the treatment with radium.

#### SUMMARY

A method of radium treatment is described which has reduced gastric acidity in cases of duodenal ulcer.

In 13 of 14 cases in which this treatment has been tried there has been a marked reduction in acidity of the gastric juice and in volume of juice secreted.

Clinical improvement accompanied chemical improvement in the majority of cases.

NOTE.—In the interval between completion of this paper and receipt of the proof our attention has been drawn to a paper by Palmer and Templeton,<sup>4</sup> in which roentgen radiation directed toward the upper two thirds of the stomach depressed gastric secretion in patients. Observations made by other investigators who also irradiated the stomach

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4. Palmer, W. L., and Templeton, F.: The Effect of Radiation Therapy on Gastric Secretion, *J. A. M. A.* **112**:1429 (April 15) 1939.

externally are summarized. We were unaware of this work while our observations on the effect of intragastric radium therapy were in progress. The local effects on the acid secretion of the stomach and the duration of these effects following the two types of treatment appear to be similar, but in the series of patients treated by radium no adverse effects on neighboring organs were noted.

Physicians of Dunedin Hospital gave us permission to study patients under their care, Prof. F. H. Smirk assisted us in the preparation of this paper, Prof. E. F. D'Ath made the report of the microscopic examination of sections of stomach removed at operation and Miss M. N. Woods did the chemical analysis on all the specimens of gastric juice.

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# USE OF THE DAILY FECAL OUTPUT OF UROBILINOGEN AND THE HEMOLYTIC INDEX IN THE MEASUREMENT OF HEMOLYSIS

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The concentration of hemoglobin and the number of red cells in the blood are normally kept fairly constant as the result of two opposing forces: blood formation in the bone marrow and blood destruction, presumably in the reticuloendothelial system. The degree of red cell formation can be fairly well judged not only by the erythrocyte count but by such factors as polychromatophilia and the reticulocyte count or more directly by biopsy of bone marrow. The degree of blood destruction may be estimated by determination of the various hemoglobin derivatives, such as bilirubin in the blood and urobilinogen in the urine and the feces. The output of the latter pigment, which is formed directly from bilirubin in the intestines, has been shown to be useful as an index of hemoglobin destruction. On its formation in the intestines urobilinogen may be said to undergo one of three processes: (1) absorption by the intestinal mucosa into the portal circulation and the liver, where it may again be converted to bilirubin and reexcreted in the bowel ("enterohepatic circulation"); (2) absorption by the intestinal mucosa into the general circulation and eventual excretion (as urobilinogen) in the urine (the normal daily urinary excretion is 1 to 2 mg.), or (3) excretion in the feces (the bulk of urobilinogen is removed in this way). Urobilin is the collective name for several oxidation forms of urobilinogen.

The daily amount of urobilinogen excreted in the feces (50 to 200 mg.) shows great fluctuation, due in part to the rather complicated endogenous metabolism of urobilinogen and in part to variations in the intestinal motility. There are, furthermore, marked individual differences which are chiefly dependent on the total mass of circulating hemoglobin. This last-named value is obtained from the concentration

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This investigation was aided by grants from the Charlton Fund, Tufts College Medical School and the Dazian Foundation.

of hemoglobin in grams per hundred cubic centimeters and from the total blood volume. The latter varies directly, as does the basal metabolic rate, with the surface area of the subject. Thus, to some extent at least, the daily output of urobilinogen in the feces is an expression of the surface area, and this measurement must be taken into account in its evaluation. Since the only source of fecal urobilinogen is the hemoglobin of destroyed red cells, calculation of the mathematic relation between the excreted pigment and the total mass of hemoglobin should be a more reliable indicator of the degree or rapidity of hemolysis than the fecal content of urobilinogen alone. Such a hemolytic index may be expressed by the following equation:

$$\frac{\text{average (of 4 days) daily output of fecal urobilinogen (mg.)} \times 100}{\text{total hemoglobin (hemoglobin [Gm./100 cc.]} \times \frac{\text{total blood volume}}{100}}$$

This index furnishes information regarding the amount of excreted urobilinogen derived daily from 100 Gm. of circulating hemoglobin.

As just stated, the daily output of fecal urobilinogen in a given subject is irregular. Singer<sup>1</sup> showed that a fairly constant daily rate could be attained by keeping the subject on a constant diet. The irregular excretion of urobilinogen during the period of a freely chosen diet could be leveled out by taking average daily values, which over a ten day period coincided closely with the values obtained with the subject on a constant diet. It was determined in this study that the minimal period for estimation of a fairly good daily average was four days, a single day's estimation being practically valueless. In the presence of diarrhea, constipation or fever even the daily average of a four day period may be grossly inaccurate. Recently Sparkman<sup>2</sup> has used single fecal specimens for the determination of urobilinogen per hundred grams of stool. Because this method takes no account of the intricacies of urobilinogen metabolism and variations in its output, it is, as Watson<sup>3</sup> has already pointed out, subject to great inaccuracy.

Thus, for determination of the "hemolytic index," it is necessary to obtain the average daily output of urobilinogen in a complete four day collection of feces and to determine the blood volume. Although introduced by Belanogowa<sup>4</sup> in 1928, determination of this or a similar index

1. Singer, K.: Studien zum Problem der Blutmauserung: I. Ueber den Einfluss der Ernährung auf die Urobilinogen-Ausscheidung mit den Faeces, Wien. Arch. f. inn. Med. **20**:59, 1930; II. Ueber den Einfluss der Leberdiät auf die Funktion des erythrolytischen Systems, Ztschr. f. d. ges. exper. Med. **71**:137, 1930.

2. Sparkman, R.: Studies of Urobilinogen: II. Normal Values for Excretion of Urobilinogen, Arch. Int. Med. **63**:867 (May) 1939.

3. Watson, C. J.: Regurgitation Jaundice, J. A. M. A. **114**:2427 (June 22) 1940.

4. Belanogowa, N. S.: Ueber den Blutumsatz bei verschiedenen Anämien und die Beeinflussung desselben durch die Behandlung mit Bluttransfusionen, Salvarsan, Arsen, Eisen und Leberdiät, Deutsches Arch. f. klin. Med. **162**:297, 1928.



has been used in comparatively few investigations. The present paper deals with our use of this method, which we have found particularly helpful in the study and evaluation of the hemolytic syndromes.

### METHODS

*Red Cell Count.*—Pipets and hemocytometers certified by the United States Bureau of Standards and an automatic pipet shaker were used.

*Hemoglobin:* An Evelyn or a Cenco photoelectric colorimeter was used.<sup>5</sup> One hundred per cent equals 15.6 Gm. per hundred cubic centimeters of blood.

*Hematocrit Reading.*—Venous blood was collected in 5 cc. vials containing 6 mg. of dry ammonium oxalate and 4 mg. of potassium oxalate<sup>6</sup> and was centrifuged in Wintrobe hematocrit tubes for twenty-five minutes at 3,500 revolutions per minute.

*Blood Volume.*—The method of Gibson and Evans<sup>7</sup> using the azo dye Evans blue was employed. When actual volumes were not determined, the "expected" total volumes were used in determining the circulating hemoglobin values.

*"Expected" Blood Volume.*—This factor was determined by the formula of Gibson and Evans,<sup>7</sup> which is based on the surface area and is applicable when no marked disturbance in the height to weight relation exists. Otherwise, the blood volume is related to the weight.

*Fecal Urobilinogen.*—The urobilinogen in the feces was determined quantitatively, according to the method of Watson.<sup>8</sup> This method is based on the original method of Terwen<sup>9</sup> and the modification of Fürth and Singer.<sup>10</sup> The average daily value of a four day collection was used.

*Quantitative Measurement of Bilirubin.*—The method of Malloy and Evelyn<sup>11</sup> was used. Evelyn and Cenco photoelectric colorimeters were used.

### RESULTS

*Normal Subjects* (table 1).—The hemolytic index in 8 normal adults varied from 11.1 to 20.8; this indicates that at least 11.1 mg. of urobilinogen is normally derived from 100 Gm. of hemoglobin. Similar

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5. Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63, 1936.

6. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777, 1934.

7. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

8. Watson, C. J.: The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931.

9. Terwen, A. S. L.: Ueber ein neues Verfahren zur quantitativen Urobilinbestimmung in Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:92, 1925.

10. Fürth, O., and Singer, K.: Ueber die quantitative Bestimmung kleiner Urobilinogen- und Urobilinnengen in den Faeces, Ztschr. f. d. ges. exper. Med. **69**:152, 1929.

11. Malloy, H. T., and Evelyn, K. A.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with the Photoelectric Colorimeter, J. Biol. Chem. **122**:597, 1938.

TABLE 1.—Normal Controls

Case No.	Red Cell Count	Hemo-globlin, %	Color Index	Hemato-crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circulating Hemo-globin, Gm.	Daily Fecal Urobilin-nogen, Mg.	Hemolytic Index, Mg. Uro-bilinogen per 100 Gm. Hemoglobin	Serum Bilirubin, Mg. per 100 Cc.
					Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	5,100,000	97	0.95	48	1,977	2,193	4,170	1,914	2,071	3,985	598	66.2	11.1	0.47
2	4,800,000	95	0.99	41	1,763	2,337	4,100	1,991	2,540	4,531	667	75.0	11.2	0.43
3	5,600,000	100	0.91	47.5	2,475	3,025	5,500	2,380	2,620	4,800	749	85.6	11.4	....
4	4,600,000	94	1.02	41	2,295	2,805	5,100	1,966	2,830	4,796	700	86.5	12.3	0.88
5	4,600,000	90	1.00	41	1,484	1,966	3,450	1,222	1,733	2,955	511	68.0	13.3	....
6	5,700,000	111	0.97	49	2,637	3,223	5,860	2,660	2,770	5,430	934	180.0	19.2	0.47
7	4,400,000	83	0.98	39	1,627	2,023	3,650	1,375	2,125	3,400	452	92.1	20.3	0.87
8	4,500,000	85	0.91	44.5	2,070	2,530	4,600	2,051	2,558	4,609	508	105.5	20.8	0.40

TABLE 2.—Hypochromic Anemia

Case No.	Red Cell Count	Hemo-globlin, %	Color Index	Hemato-crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circulating Hemo-globin, Gm.	Daily Fecal Urobilin-nogen, Mg.	Hemolytic Index, Mg. Uro-bilinogen per 100 Gm. Hemoglobin	Serum Bilirubin, Mg. per 100 Cc.
					Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	3,700,000	51	0.69	33.7	1,485	1,815	3,300	1,106	2,295	3,461	277	11.2	4.0	0.19
2	4,900,000	47	0.48	31.3	1,763	2,337	4,100	1,250	2,750	4,000	296	18.0	6.1	0.48
3	3,800,000	62	0.82	31.0	1,755	2,145	3,900	1,262	2,810	4,072	390	35.0	9.0	0.50
4*	4,700,000	78	0.83	39.5	1,845	2,155	4,000	1,136	1,740	2,876	351	16.8	4.8	0.59
5	3,400,000	63	0.78	20.5	1,720	2,280	4,000	645	2,663	3,308	274	19.5	7.1	0.40

Case No.	Minimal Expected Fecal Urobilinogen, Mg.	Maximal Expected Fecal Urobilinogen, Mg.	Actual Fecal Urobilinogen, Mg.	Reduction from Minimal Value, %
1	30.7	57.6	11.2	64
2	32.9	61.6	18.0	46
3	43.3	81.1	35.0	19
4	39.0	72.9	16.8	57
5	30.4	57.0	19.5	36

\* Myxedema.

values (10.3 to 22.8) were obtained by Heilmeyer and Oetzel<sup>12</sup> on the basis of 100 per cent hemoglobin being equal to 16.5 Gm. Corrected for 15.6 Gm. their values are 10.9 to 24.2. In children Josephs<sup>13</sup> found a somewhat higher urobilinogen-hemoglobin ratio. His values are not directly comparable to ours because he used a different method for determination of urobilinogen.

*Conditions with a Lowered Hemolytic Index.*—In cases of several disorders which differed greatly in character—chronic hypochromic (iron deficiency) anemia, polycythaemia vera and the postsplenectomy state—a hemolytic index definitely lower than normal was demonstrable. A low hemolytic index indicates (*a*) a diminished rate of hemolysis in comparison with the normal rate, (*b*) a sparing action of the body in output of the pigment or (*c*) a combination of both. That the organism may retain hemoglobin derivatives for the resynthesis of hemoglobin has been demonstrated by various investigators (Heilmeyer and Oetzel,<sup>12</sup> Singer<sup>1</sup> and others).

*Iron Deficiency Anemia:* A low index was found in 4 cases of hypochromic anemia (table 2, cases 1, 2, 3 and 4). One of the advantages of the hemolytic index is that one may set up in any given case minimal and maximal expected values for output of urobilinogen. The actual output can then be expressed in percentage of the expected figures, thus showing more clearly the deviation from the normal. In the cases of hypochromic anemia the actual reduction in the pigment output was 19 to 64 per cent. This may be partly due to a sparing action of the body in the output of pigment in the presence of a deficiency of hemoglobin, although an actual diminution in the rate of blood destruction is probably also present.

*Polycythemia:* In 6 of 7 cases of polycythaemia vera, the hemolytic index was definitely low (table 3), with the expected minimal excretion of urobilinogen reduced 17 to 45 per cent. In all cases there was the characteristic considerable increase of the total blood volume and the red cell mass. The lowered hemolytic index in these cases of polycythemia points either to a decreased breakdown of the red cells or to a sparing of pigment by the body for use in hemoglobin formation. The latter interpretation seems most likely. A similar sparing mechanism was demonstrated by Jacobs and Scheffner<sup>14</sup> and Singer<sup>1</sup> after the

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12. Heilmeyer, L., and Oetzel, W.: Blutfarbstoffwechselstudien: II. Ergebnisse bei Gesunden; Diätversuche; Der Blutfarbstoffwechsel im Hunger, Deutsches Arch. f. klin. Med. **171**:365, 1931.

13. Josephs, H. W.: The Mechanism of Anemia in Infancy, Bull. Johns Hopkins Hosp. **55**:335, 1934.

14. Jacobs, E., and Scheffner, W.: Quantitative Urobilinogenbestimmungen im Stuhle, Ztschr. f. d. ges. exper. Med. **44**:116, 1924.

TABLE 3.—*Polycythemia*

Case No.	Red Cell Count	Hemo- globin, %	Color Index	Hemato- crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circu- lating Hemo- globin, Gm.	Daily Fecal Urobili- nogen, Mg.	Hemolytic Index, Mg. Uro- bilinogen per 100 Gm. Hemoglobin	Serum Bili- rubin, Mg. per 100 Cc.
					Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	7,800,000	128	0.82	67	1,699	2,251	3,950	3,997	2,032	6,029	1,170	198.9	17.0	....
2	7,400,000	89	0.60	56	1,677	2,263	3,900	3,196	2,809	6,065	837	74.3	8.8	0.40
3	6,400,000	119	0.93	55	2,408	2,942	5,350	3,564	2,911	6,475	1,204	79.1	6.6	....
4	6,800,000	98	0.72	56	1,935	2,565	4,500	3,290	2,620	5,910	893	83.0	9.2	0.48
5	7,300,000	101	0.69	55.5	2,250	2,750	5,000	3,830	3,397	7,227	1,135	77.0	6.8	1.60
6	7,900,000	131	0.83	64	2,520	3,080	5,600	4,665	2,823	7,488	1,528	94.2	6.2	0.01
7	6,400,000	113	0.88	57	1,600	2,120	3,720	3,512	2,650	6,162	1,085	75.4	6.9	0.98

Case No.	Minimal Expected		Maximal Expected		Actual Fecal Urobilinogen, Mg.	Reduction from Expected Minimal Value, %	
	Fecal Urobilinogen, Mg.	Feecal Urobilinogen, Mg.	Fecal Urobilinogen, Mg.	Feecal Urobilinogen, Mg.			
1	129.9	129.9	242.9	198.9	Increase		
2	92.9	92.9	173.7	74.3	20		
3	133.6	133.6	249.8	79.1	41		
4	99.7	99.7	186.4	83.0	17		
5	126.0	126.0	235.6	77.0	39		
6	169.6	169.6	317.1	94.2	45		
7	120.4	120.4	225.7	75.4	38		

injection of phenylhydrazine into patients and into experimental animals. Otto and Heilmeyer<sup>15</sup> also demonstrated slightly diminished values for the hemolytic index in 2 cases of polycythemia, and this has also been confirmed by Watson (personal communication). The presence of a low hemolytic index definitely rules out the possibility that the stimulus for the overproduction of red cells in cases of this disease lies in a primary hemolytic process with overcompensation by the bone marrow.

*Postsplenectomy State:* A lowered hemolytic index was found in 10 of 13 cases (table 4) in which splenectomy had been performed for various diseases, such as purpura, traumatic rupture of the spleen, cirrhosis of the liver, hemolytic anemia, leukemia and Gaucher's disease. The reduction from the expected minimal output varied from 20 to 69 per cent. With 2 exceptions, no great deviations from the expected total blood volume were encountered. In these cases there were also other changes, such as target cells, Howell-Jolly bodies and increased hypotonic resistance, as discussed in another paper.<sup>16</sup> The reduction in output of fecal urobilinogen became evident shortly after splenectomy and was persistent, indicating a definite diminution in blood destruction. In the 3 cases in which the hemolytic index was normal it was apparent that increased hemolysis had persisted after splenectomy. In 2 of these cases there was continued hemolytic anemia and marked spherocytosis despite splenectomy. In the third case well advanced Gaucher's disease was present.

*Conditions with an Increased Hemolytic Index.*—Determination of the hemolytic indexes in instances of increased hemolysis was of particular importance, both from the clinical and the theoretic standpoint. In some cases although the absolute value for urobilinogen output in the feces was practically normal, the rate of blood destruction as measured by the hemolytic index was greatly increased.

*Pernicious Anemia:* Of 3 cases of pernicious anemia (table 5) in which the bilirubin content of the serum was normal (0.5 to 1.0 mg. per hundred cubic centimeters), the absolute urobilinogen output in the feces in 2 cases was only slightly increased (236 and 266 mg. per day). Determination of the hemolytic index, however, demonstrated a greatly increased rate of hemolysis, namely, 204 to 474 per cent above the expected maximal figures! The comparatively low absolute values for fecal urobilinogen were dependent on the lowered mass of circulating hemoglobin; reference to the hemolytic index indicated, however, that

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15. Otto, W., and Heilmeyer, L.: *Klinische Farbmessungen: X. Der Einfluss von Phenylhydrazingaben und Aderlässen auf den Blutfarbstoffwechsel mit besonderer Berücksichtigung der Harnfarbstoffausscheidung*, Ztschr. f. d. ges. exper. Med. **77**:144, 1931.

16. Singer, K.; Miller, E. B., and Dameshek, W.: *Hematologic Changes Following Splenectomy in Man*, Am. J. M. Sc. **202**:171, 1941.

TABLE 4.—*Postsplenectomy State*

Case No.	Red Cell Count	Hemo-globin, %	Color Index	Hemato-erit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circulating Hemo-globin, Gm.	Daily Fecal Urobilin-nogen, Mg.	Hemolytic Index, Mg. Uro-bilinogen per 100 Gm. Hemoglobin	Serum Bilirubin, Mg. per 100 Cc.
					Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	4,800,000	84	0.88	42	2,295	2,305	5,100	1,961	3,029	4,990	649	22.2	3.4	0.32
2	5,400,000	77	0.71	45	1,971	2,409	4,380	1,781	2,342	4,123	495	17.0	3.6	0.38
3	5,300,000	85	0.80	44.5	1,763	2,337	4,100	1,442	1,929	3,371	445	25.2	5.0	0.30
4	3,700,000	65	0.88	37.0	2,365	3,135	5,500	2,004	3,413	5,417	547	31.3	5.7	0.97
5	4,600,000	91	0.99	43	1,670	2,080	3,650	2,270	2,020	5,290	750	45.8	6.1	0.37
6	4,900,000	92	0.94	43	1,711	2,269	3,980	1,703	2,258	3,961	506	37.5	6.5	0.77
7	5,300,000	102	0.96	44	1,710	2,090	3,800	1,447	1,919	3,366	535	38.5	7.2	0.90
8	4,800,000	94	0.98	43	2,340	2,860	5,200	2,231	3,057	5,289	767	58.3	7.5	0.88
9	4,900,000	96	0.98	48	2,520	3,080	5,600	2,556	2,770	5,326	794	55.0	8.0	0.38
10	5,300,000	102	0.96	48	2,412	2,948	5,360	2,419	2,728	5,147	818	72.9	8.9	0.50
11	3,800,000	85	1.12	38.5	1,729	2,291	4,020	1,452	2,320	3,772	498	69.7	14.0	0.97
12	4,200,000	68	0.79	36	936	1,144	2,080	695	1,263	1,958	202	29.4	14.6	0.37
13	5,000,000	96	0.96	45	1,733	2,297	4,030	1,704	2,169	3,873	531	86.4	14.8	0.95

Case No.	Minimal Expected Fecal Urobilinogen, Mg.		Maximal Expected Fecal Urobilinogen, Mg.		Actual Fecal Urobilinogen, Mg.	Reduction from Expected Minimal Value, %	
	Minimal	Expected	Maximal	Expected			
1	72.0	135.0	22.2	69			
2	54.9	103.0	17.6	68			
3	40.4	92.6	25.2	49			
4	60.7	113.5	31.3	40			
5	83.3	157.8	45.8	45			
6	63.8	117.4	37.5	40			
7	59.4	111.1	38.5	35			
8	86.1	159.1	53.3	31			
9	88.1	164.7	55.0	38			
10	90.8	169.8	72.9	20			
11	55.3	103.4	69.7	Increase			
12	22.4	41.9	29.4	Increase			
13	64.5	120.6	86.4	Increase			

TABLE 5.—*Pernicious Anemia in Relapse*

Case No.	Red Cell Count	Hemo- globin, %	Color Index	Hemato- crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circu- lating Hemo- globin, Gm.	Daily Fecal Urobili- nogen, Mg.	Hemolytic Index, Mg. Uro- bilinogen per 100 Gm. Hemoglobin	Serum Bili- rubin, Mg. per 100 Cc.
					Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	1,900,000	50	1.32	20	1,720	2,030	3,750	500	2,060	2,560	198	236	119.2	0.57
2	900,000	26	1.44	13	1,860	2,180	4,040	460	3,290	3,750	135	346	230.6	0.87
3	.....	68	....	36	2,016	2,464	4,480	1,394	2,624	4,018	422	366	53.1	0.72
4*	1,300,000	33	1.27	13	1,720	2,280	4,000	.....	.....	.....	208	200	96.0	....

Case No.	Minimal Expected		Maximal Expected		Actual Fecal Urobilinogen, Mg.	Increase Over Expected Maximal Value, %	
	Fecal Urobilinogen, Mg.	Fecal Urobilinogen, Mg.	Fecal Urobilinogen, Mg.	Fecal Urobilinogen, Mg.			
1	22.0	41.1	236	474			
2	15.0	28.1	346	1,131			
3	46.8	87.5	266	204			
4	23.1	43.3	200	369			

\* Achromic anemia.

these values were considerably higher than the expected normal ones. The result of the bilirubin excretion test, which was performed in all 3 cases, was normal, indicating a normal (or perhaps better than normal) excretion of bilirubin by the liver cells. In a fourth case of pernicious anemia, atypical because of the presence of free hydrochloric acid in the gastric juice and an unusually slow response to liver extract ("achrestic" anemia of Wilkinson and Israëls), the hemolytic index was also greatly increased. These observations serve to indicate that a normal bilirubin level may occur in the presence of increased hemolysis. In cases of severe anemia demonstration of the presence and the degree of increased hemolysis may only be possible by means of the hemolytic index.

*Hemolytic Anemia:* Of 9 cases of hemolytic anemia of the congenital and acquired varieties (table 6, cases 1 through 9), an elevated hemolytic index was present in all. The increase over the maximal expected urobilinogen output varied between 287 and 1,672 per cent. No regular parallelism between the increase of the hemolytic index and the bilirubin level of the blood was demonstrable, again indicating that the bilirubin level is the product of two opposing forces, viz., bilirubin formation and bilirubin excretion by the liver cells, and that the best single evidence of increased hemolysis is the determination of the fecal output of urobilinogen (and its relation to the total mass of hemoglobin). The extreme reduction in output of urobilinogen following splenectomy was striking.

*Cooley's Anemia:* In 2 cases of Mediterranean anemia (table 6, cases 10 and 11) a definitely elevated hemolytic index was present. The increases over the maximal expected output of urobilinogen were 700 and 2,159 per cent, respectively. The hemolytic character of this type of anemia, although "target" cells with increased hypotonic resistance were present, indicates that the result of the fragility test is by no means indicative of the susceptibility of the red cells to hemolysis.

*Gaucher's Disease:* In a case of Gaucher's disease (table 6, case 12) in which the bilirubin level in the serum was high (2.98 mg. per hundred cubic centimeters), the hemolytic index was slightly increased. There was also evidence of retention jaundice, as indicated by the delay in bilirubin excretion when 50 mg. of bilirubin was injected intravenously. When the spleen was removed, the jaundice quickly disappeared. These findings indicated that increased hemolysis (splenic in type) may be present in Gaucher's disease.

#### COMMENT

Of the various indexes which might point to increased destruction of blood—jaundice of the acholuric type, "indirect" bilirubinemia, an increase in the urinary urobilinogen, anemia, leukocytosis and reticulo-



TABLE 6.—*Hemolytic Anemia*

Case No.	Diagnosis	Red Cell Count	Hemo- globin, %	Color Index	Hemato- crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circu- lating Hemo- globin, Gm.	Daily Fecal Urobili- nogen, mg.	Hemolytic Index, Mg. Uro- bilinogen per 100 Gm. Hemoglobin	Serum Bili- rubin, Mg. per 100 Cc.
						Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.				
1	Congenital hemolytic anemia	2,600,000	41	0.85	21.0	1,742	2,318	4,060	891	3,351	4,242	288	690	239	2.40
2	Congenital hemolytic anemia	4,100,000	82	1.00	35.0	1,485	1,815	3,300	1,363	2,454	3,720	476	884	186	2.40
3	Congenital hemolytic anemia	3,100,000	49	0.79	27.0	401	612	1,073	.....	.....	.....	81.3	113	139	Not visibly jaundiced
4	Congenital hemolytic anemia	3,500,000	57	0.81	29.0	453	601	1,054	.....	.....	.....	94.0	75	79	1.20
5	Acquired hemolytic anemia	3,600,000	68	0.94	29.0	956	1,169	2,125	.....	.....	.....	223	625	280	4.40
6	Acquired hemolytic anemia	2,500,000	46	0.92	26.0	2,655	3,245	5,900	1,206	3,821	5,027	357	1,313	367	4.26
7	Acquired hemolytic anemia	2,900,000	58	1.00	23.5	1,733	2,297	4,030	910	3,060	4,000	360	631	172	3.95
8	Acquired hemolytic anemia	2,200,000	57	1.32	26.0	1,656	2,194	3,850	913	2,830	3,773	332	465	149	0.82
9	Acquired hemolytic anemia	1,700,000	32	0.94	17.0	1,763	2,337	4,100	826	4,036	4,862	243	1,925	792	0.65
10	Cooley's anemia.....	4,300,000	67	0.78	35.0	2,318	2,832	5,150	.....	.....	.....	536	890	166	2.40
11	Cooley's anemia.....	2,100,000	27	0.64	14.0	696	851	1,547	.....	.....	.....	65	305	469	Visibly jaundiced
12	Gaucher's disease.....	5,250,000	93	0.88	45.0	2,583	3,107	5,690	.....	.....	.....	819	275	33.5	2.98

Case No.	Minimal Expected Fecal Urobilinogen, Mg.	Maximal Expected Fecal Urobilinogen, Mg.	Actual Fecal Urobilinogen, Mg.	Increase Over Maximum Value, %
1	32.0	59.8	690	1,054
2	52.8	98.7	889	793
3	9.0	16.8	113	573
4	10.4	19.4	75	287
5	24.8	46.4	625	1,247
6	39.6	74.1	1,313	1,672
7	40.0	74.8	621	730
8	36.9	69.0	495	617
9	27.0	50.5	1,925	3,712
10	69.5	111.3	890	700
11	7.2	13.5	305	2,159
12	91.0	170.4	275	61

TABLE 7.—Comparison of Data Taken Before and After Splenectomy

Case No.	Date	Diagnosis	Red Cell Count	Hemo- globin, %	Color Index	Hemato- crit Reading, %	Expected Blood Volumes			Determined Blood Volumes			Total Circu- lating Hemo- globin, Gm.	Daily Fecal Urobili- nogen, Mg.	Hemolytic Index, Mg. Uro- bilinogen per Bil- rubin, 100 Gm. Hemo- globin 100 Cc.
							Red Cells, Cc.	Plasma, Cc.	Total, Cc.	Red Cells, Cc.	Plasma, Cc.	Total, Cc.			
7, table 4	10/30/39	Before splenectomy; con- genital hemolytic anemia	4,100,000	82	1.00	35.0	1,485	1,815	3,300	1,260	2,454	3,720	476	884	186 2.49
	1/30/40	After splenectomy.....	5,300,000	102	0.96	44.0	1,710	2,090	3,800	1,447	1,919	3,366	535	38.5	7.2 0.90
3, table 4	9/20/40	Before splenectomy; thrombopenic purpura	5,300,000	77	0.73	....	1,763	2,337	4,100	.....	.....	.....	...	63.9	... ....
	11/13/40	1 mo. after splenectomy	5,300,000	85	0.80	44.5	1,763	2,337	4,100	1,442	1,929	3,371	445	25.2	5.6 0.30
13, table 1	10/16/39	Before splenectomy; ac- quired hemolytic anemia	2,900,000	58	1.00	23.5	1,733	2,297	4,030	940	3,060	4,000	360	621	172 3.95
	12/23/39	After splenectomy.....	2,100,000	45	1.07	....	1,733	2,297	4,030	.....	.....	.....	322	1,700	528 ....
	4/ 4/40	After oophorectomy.....	3,800,000	71	0.93	37.0	1,763	2,337	4,100	.....	.....	.....	451	350	77.6 0.95
	5/28/40	After oophorectomy.....	4,900,000	102	1.04	48.0	1,763	2,337	4,100	.....	.....	.....	652	80.1	12.3 0.60

cytosis—none is specific. As Dameshek and Singer<sup>17</sup> have shown, acholuric jaundice and “indirect” bilirubinemia may be present in “familial nonhemolytic jaundice” and in mild degrees of hepatic disease. The importance of determining the fecal output of urobilinogen in the differential diagnosis of familial hemolytic jaundice and the nonhemolytic type was emphasized in this paper. An increase in urinary excretion of urobilinogen is not only common in mild disease of the liver but is present in acute infections. The excretion of urobilinogen in the urine is furthermore extremely variable in the hemolytic syndromes. In some conditions with marked hemolysis the values for urinary urobilinogen may be only slightly above normal. Anemia and leukocytosis, with or without reticulocytosis, are, of course, nonspecific and may be associated with hemorrhage, infection, acute leukemia, malignant growths, etc. Spherocytosis and an increase in fragility of red cells in hypotonic solutions of sodium chloride, which, as Dameshek and Schwartz<sup>18</sup> have emphasized, are definite indicators of the presence of a hemolytic process, are often not present in a given case, particularly in an instance of the acquired type of hemolytic anemia. What is more, spherocytosis is usually present after splenectomy in cases of congenital hemolytic jaundice, although there is no evidence of increased breakdown of the blood.

In our experience the only constant indicator of increased hemolysis—with or without anemia, jaundice, reticulocytosis, increased urinary urobilinogen, etc.—is an increase in the fecal content of urobilinogen. Even this, as just pointed out, may be defective when the mass of circulating hemoglobin is so diminished that the absolute content of urobilinogen in the feces is normal or low, even though hemolysis is increased. Under such circumstances the hemolytic index becomes all important.

Determination of the hemolytic index requires estimation of the blood volume. This is a relatively difficult procedure which is not applicable to routine laboratory usage. In the present investigation the Gibson-Evans dye method for estimating the blood volume was used. This method has been shown to be more accurate than previous dye methods, since the blue dye can be read accurately in the photo-electric colorimeter, even in the presence of slight hemolysis.<sup>19</sup>

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17. Dameshek, W., and Singer, K.: Familial Nonhemolytic Jaundice, *Arch. Int. Med.* **67**:259 (Feb.) 1941.

18. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia, *Medicine* **19**:231, 1940.

19. That, strictly speaking, the red cell volume or the total hemoglobin content may not be as accurate as Gibson and others have intimated has recently been pointed out by Ebert and Stead (Ebert, R. V., and Stead, E. A.: Demonstration

An approximation of the total blood volume ("expected" blood volume) is obtained by having recourse to the formula of Gibson and Evans,<sup>7</sup> which is based on the surface area. From knowledge of this factor and the hematocrit reading, the red cell mass, or total hemoglobin, can be readily determined. An even simpler, albeit more inaccurate, approximation may be made from the concentration of hemoglobin or the hematocrit readings. Thus with a hemoglobin percentage of 20 (one fifth of normal) and a normal output of urobilinogen, one may say with fair assurance that the hemolytic index is at least five times normal. In a child weighing 50 pounds (23 Kg. [approximately one-third the weight of a normal adult]) with a hemoglobin concentration of 20 per cent and a daily fecal output of urobilinogen of 200 mg., blood destruction is at least fifteen times greater than normal.

From the results thus far obtained, it is evident that the hemolytic index permits a better evaluation of the pigment metabolism than does simply the absolute value of the daily excretion of urobilinogen. Knowledge of the index permits the expression of any given urobilinogen excretion in percentage of the expected minimal or maximal values. This is of definite value in the interpretation of the output of pigment in the various blood disorders.

A reduced hemolytic index, such as occurs in chronic hypochromic anemia, in polycythemia and in the postsplenectomy state, may be due to a diminished rate of blood destruction, to a sparing of the pigment by the body or to a combination of both. The first mechanism appears to be present in the postsplenectomy state and is confirmatory of the role of the spleen in blood destruction. In polycythemia a pigment-sparing action of the body is probable. That the organism tries to prevent the loss of pigment complexes in certain pathologic conditions was demonstrated in pigment balance studies following the injection of phenylhydrazine. Jacobs and Scheffner<sup>14</sup> computed that only one third of the expected urobilinogen was actually excreted and Singer<sup>1</sup> found only one fifth of the expected urobilinogen in the feces of dogs after a single injection of phenylhydrazine. In the anemia of chronic iron deficiency the lower index may also be due to a sparing action by the body, although a diminished rate of blood destruction must also be taken into consideration, since in cases of such anemia target cells and decreased fragility of red cells occasionally occur, as in the postsplenectomy state.

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That in Normal Man No Reserves of Blood Are Mobilized by Exercise, Epinephrine and Hemorrhage, *Am. J. M. Sc.* **201**:655, 1941), who demonstrated that although the plasma volumes may be accurately determined, the red cell volumes (which depend for their calculation on the hematocrit reading) are subject to some variation, depending on the different concentrations of red cells in the various parts of the circulation.

In hemolytic anemias determination of the hemolytic index is particularly valuable in cases in which the absolute values of the urobilinogen output are only slightly above normal. By relating these values to the hemoglobin content a considerable degree of hemolysis may be demonstrated. This was particularly evident in 4 cases of pernicious anemia in which the blood level of bilirubin was normal. In these cases the hemolytic index was the only means for obtaining an estimation of the degree of hemolysis. The marked diminution in blood destruction following the use of liver extract is a striking phenomenon. The finding of an elevated hemolytic index in 2 cases of Cooley's anemia, despite the presence of target cells with increased resistance to hypotonic solution of sodium chloride indicates that although the target cell presents an increased resistance to such solutions in the test tube, its intravascular resistance may be distinctly altered. The mechanisms which lead to increased blood destruction in Cooley's anemia are still obscure and may be concerned with fundamental problems of hemoglobin metabolism. The variations in hemolytic index during the course of hemolytic jaundice have been of material assistance in assaying the severity of the disease. The great reduction in hemoglobin destruction following splenectomy has been of unusual interest. As already pointed out, much less hemoglobin is destroyed per unit of time in the patient who has undergone splenectomy than in the normal person. This may also be the case, even with persistent spherocytosis and increased fragility of red cells in hypotonic saline solution, in instances of congenital hemolytic jaundice.

Since the results of our studies have demonstrated that even the average daily urobilinogen output of a four day collection of feces may of itself be unrevealing or even misleading as regards the question of increased blood destruction, the questionable value of determining the amount of urobilinogen per hundred grams of stool in a single specimen (Sparkman<sup>2</sup>) should be evident. The amount of urobilinogen excreted daily should be known, and to have even greater significance, this figure should be related to the values for hemoglobin, red cell count, hematocrit reading and—whenever possible—to the total mass of circulating hemoglobin.

#### SUMMARY

1. Determination of the average daily output of urobilinogen in the feces has proved of great value in the diagnosis and the follow-up study of various blood dyscrasias, particularly in those conditions associated with increased blood destruction.

2. Since the daily fecal output of urobilinogen depends on the total mass of circulating hemoglobin, it is important to relate the former to the latter. This is done in the "hemolytic index," which shows

that 11.1 to 20.8 mg. of fecal urobilinogen is normally derived from 100 Gm. of circulating hemoglobin in twenty-four hours.

3. In the presence of anemia or of a small surface area (as in children) the hemolytic index may show a greatly increased rate of blood destruction, although the absolute content of urobilinogen may be normal. This is particularly evident in certain types of hemolytic anemia and in pernicious anemia. In instances of the latter disease it is not uncommon to find a normal level of bilirubin in the blood with a greatly increased hemolytic index.

4. Of the various indexes of possibly increased hemolysis—acholuric jaundice, "indirect" bilirubinemia, an increase in urinary excretion of urobilinogen, anemia and leukocytosis—none is specific. An increase in the fecal output of urobilinogen or in the hemolytic index is unequivocal evidence of an increased breakdown of blood.

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# FUNCTION OF THE SEPARATE KIDNEYS IN HYPERTENSIVE SUBJECTS

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The presence of a unilateral pyelographic abnormality in a hypertensive subject has been accepted as having etiologic significance, the assumption being that an abnormal pyelogram is indicative of a pathologic change resulting in obstruction to the renal blood flow and that the resulting ischemic renal tissue is responsible for elevated blood pressure.

This report is concerned with the correlation of pyelography and renal function in the separate kidneys of 21 hypertensive subjects. In addition, the effect on renal function of operative procedures designed to increase the renal blood flow will be reported for a small group of hypertensive subjects.

## SELECTION OF SUBJECTS

Twenty-one subjects with well established essential hypertension were chosen at random from the hypertension and nephritis clinic of the New York University Medical Clinic and from the wards of the Third (New York University) Medical Division of Bellevue Hospital, without regard to the presence or absence of signs or symptoms of unilateral renal disease. It should be noted that this group selected by chance did not include any subject with an advanced destructive renal lesion. A second group included 3 subjects with hypertension, each of whom had undergone one of the following operative procedures: unilateral renal omentopexy, unilateral nephropexy and bilateral splachnicectomy.

## METHODS

The methods described by Smith, Goldring and Chasis<sup>1</sup> for determining the effective renal blood flow (diodrast clearance,  $C_D$ ) and the tubular excretory mass ( $Tm_D$ ) by the excretion of diodrast at low and at high plasma levels were applied to measure these functions in the separate kidneys of these hypertensive subjects. Each subject was examined cystoscopically, and a multiple-eyed, large-sized, usually number 8F flute-tipped catheter was passed 12 cm. up each ureter. An infusion

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This investigation was aided by a grant from the Commonwealth Fund.

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1. Smith, H. W.; Goldring, W., and Chasis, H.: Measurement of the Tubular Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J. Clin. Investigation* **17**:263-278 (May) 1938.

of phenolsulfonphthalein, inulin and diodrast was given according to the usual clearance technic.<sup>1</sup> After observation of the ureteral orifices to detect extra-catheter leakage, the cystoscope was withdrawn and a urethral catheter inserted into the bladder. The appearance time of phenolsulfonphthalein was noted, and samples of urine obtained from each kidney were weighed to determine the specific gravity. The bladder was washed at intervals to detect leakage. Immediately after the functional studies, retrograde pyelograms were made with the subject in the supine and the erect position.

Renal blood flow and tubular excretory mass were measured in 10 of these subjects both by the ureteral catheter and by the bladder catheter technic, the results of both methods agreeing satisfactorily. These observations therefore indicate that introduction of a ureteral catheter does not alter the renal blood flow, the glomerular filtration rate or the tubular excretory mass.<sup>2</sup>

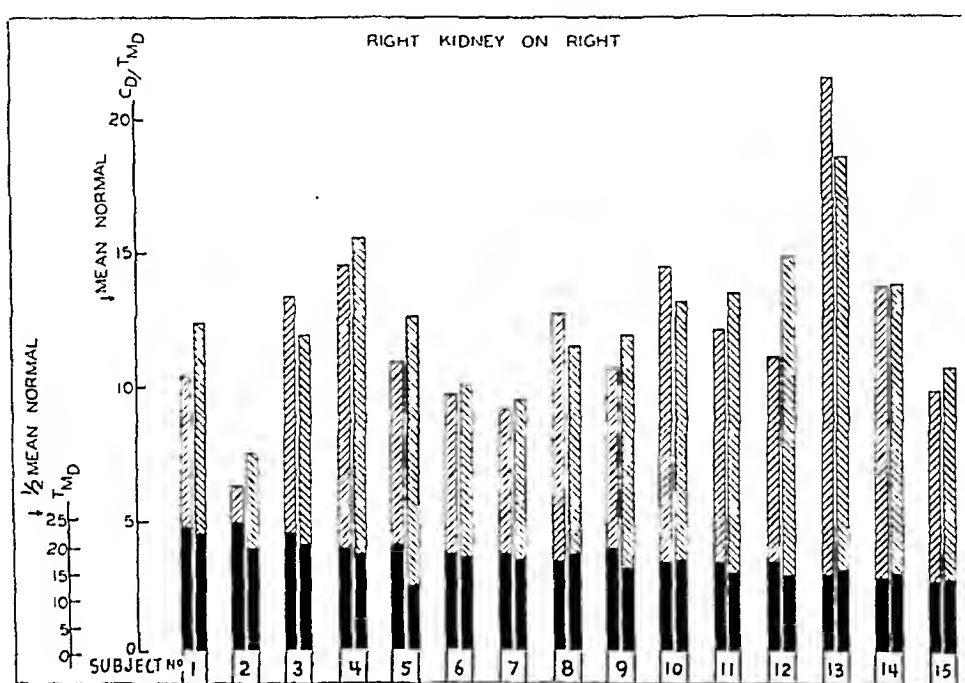


Fig. 1.—A comparison of the renal blood flow per unit of tubular excretory mass in the separate kidneys of 15 hypertensive subjects.

## RESULTS

*Effective Renal Blood Flow.*—In figure 1 the renal plasma flow ( $C_D$ ) per unit of tubular excretory mass ( $T_{mD}$ ) in each kidney of 15 hypertensive subjects is shown. The arrows represent the mean normal values of these two factors. The mean normal value of the ratio of the two factors is  $13.4 \pm 1.4$ <sup>3</sup>; values significantly below this figure indicate

2. Chasis, H., and Redish, J.: Renal Blood Flow in the Separate Kidneys of Hypertensive Subjects, *J. Clin. Investigation* 20:655-661 (Nov.) 1941.

3. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Relations of Effective Renal Blood Flow and Glomerular Filtration to Tubular Excretory Mass in Normal Man, *J. Clin. Investigation* 19:737-750 (Sept.) 1940.



*Pyelographic and Functional Data on the Separate Kidneys in  
Hypertensive Subjects\**

Subject No.	Age, Years	Range of Blood Pressure, Mm. Hg, Systolic-Diastolic	Tubular Excretory Mass, Mg. of Iodine/Min.	Effective Plasma Flow, Cc./Min.	Effective Plasma Flow/Tubular Excretory Mass	Appearance Time of Phenolsulfonphthalein, Min.	Specific Gravity of Urine	Pyelography	
								Right Kidney	Left Kidney
Subjects with Uncomplicated Hypertension									
1	53	191-110 100- 64	R.† 22.6 L.† 24.2	282 254	12.4 10.5	6.0 5.0	1.015 1.009	Low position of kidney; angulation of ureter; rotation of kidney	Low position of kidney; angulation of ureter
2	57	210-160 164- 92	R. 20.1 L. 25.0	154 182	7.7 7.3	2.5 5.0	1.011 1.011	No abnormalities	No abnormalities
3	31	192-164 126-112	R. 20.9 L. 23.4	250 315	12.0 13.4	4.0 4.0	1.037 1.035	Low position of kidney; blunting of calices	Blunting of calices
4	50	176-118 110- 86	R. 19.4 L. 20.7	294 274	15.2 13.2	5.0 5.0	1.031 1.031	No abnormalities	No abnormalities
5	37	260-186 160-106	R. 13.1 L. 20.4	166 222	12.7 10.9	4.0 4.0	1.022 1.025	No abnormalities	Bifid pelvis and double ureters
6§	26	204-176 156-114	R. 18.9 L. 19.0	194 185	10.3 9.8	2.5 4.0	1.046 1.041	No abnormalities	No abnormalities
7	52	230-192 130- 90	R. 18.9 L. 19.7	176 180	9.3 9.1	4.0 4.0	1.021 1.043	Low position of kidney; angulation of ureter	No abnormalities
8	43	158-138 100- 78	R. 21.8 L. 20.1	225 227	10.3 11.3	4.0 4.0	1.007 1.007	No abnormalities	No abnormalities
9	50	230-164 128-104	R. 16.7 L. 20.2	200 216	12.0 10.7	4.0 4.0	1.028 1.029	Calices blunted; pelvis normal; angulation and tortuosity of ureter; low position of kidney	Calices blunted; pelvis normal; angulation and tortuosity of ureter
10	55	208-174 114- 96	R. 17.4 L. 17.0	243 261	14.0 15.4	4.0 4.0	1.029 1.030	Low position of kidney	Angulation of ureter
11	39	240-190 150-120	R. 15.4 L. 17.4	211 213	13.7 12.2	7.0 2.5	1.011 1.015	No abnormalities	No abnormalities
12	51	196-160 110- 98	R. 14.8 L. 17.8	220 199	14.9 11.2	4.0 4.5	1.032 1.028	No abnormalities	No abnormalities
13	21	188-156 120- 92	R. 16.2 L. 15.2	303 330	18.7 21.7	3.0 3.5	1.012 1.013	No abnormalities	No abnormalities
14	36	236-154 160-110	R. 15.8 L. 14.8	220 205	13.9 13.8	2.5 10.0	1.026 1.020	1st degree hydronephrosis; kidney falls in erect position; ptosis of kidney; angulation of ureter	No abnormalities
15	54	210-148 126-110	R. 14.9 L. 14.7	162 146	10.8 9.9	5.0 5.0	1.021 1.021	Dilatation of calices; angulation of ureter	No abnormalities
16	55	230-180 118-108	R. L.	225 203	.... ....	4.0 3.0	1.031 1.041	Ureteropelvic junction fixed; kidney drops in erect position; ptosis of kidney; angulation of ureteropelvic junction	No abnormalities
17	49	180-120 120- 74	R. L.	225 205	.... ....	... ...	1.028 1.026	No abnormalities	No abnormalities
18	49	280-188 144-106	R. L.	205 205	.... ....	4.5 4.5	1.007 1.007	1st degree dilatation of pelvis	1st degree dilatation of pelvis
19	44	214-188 110-103	R. L.	187 173	.... ....	3.0 3.0	1.021 1.026	No abnormalities	No abnormalities
20	40	234-180 126-104	R. L.	190 173	.... ....	... ...	1.007 1.008	No abnormalities	No abnormalities
21	46	210-134 134- 90	R. L.	164 194	.... ....	5.0 5.0	1.026 1.028	No abnormalities	No abnormalities
Subjects with Hypertension Who Had Undergone Surgical Procedures for Renal Conditions									
22	44	260-152 180-100	R. 24.9 L. 12.5	276 120	11.1 9.6	3.5 3.5	1.022 1.016	No abnormalities	No abnormalities
23¶	44	182-112 124- 80	R. 13.5 L. 15.7	165 254	12.2 16.3	4.0 4.0	1.022 1.027	Angulation of ureter; ptosis of kidney; 1st degree hydronephrosis	No abnormalities
24#	17	174-150 116- 96	R. L.	252 190	.... ....	... ...	1.008 1.006	No abnormalities	Kidney rotated; calices and pelvis normal

\* Columns 3 and 4 have been corrected to 1.73 square meters.

† Right kidney.

‡ Left kidney.

§ Toxemia of pregnancy with hypertensive neuroretinopathy in 1937; right pyelonephritis in 1938.

¶ Bilateral splenectomy in May 1939.

|| Right nephropexy in December 1938.

# Left renal omentopexy in June 1938.

a decreased plasma flow per unit of functional tubular tissue, that is, relative ischemia. This ratio has greater significance than the single datum of plasma flow, since it takes into account the variation in the mass of functioning tissue in the two kidneys caused either by normal variations in the size of kidneys or by actual loss of renal parenchyma. This is demonstrated by the results obtained on subjects 5, 22 and 2 (table), in each of whom the disparities in blood flow are related to proportionate differences in the tubular excretory mass, as indicated by the equality of the ratio between the effective renal blood flow and the factor just mentioned.

It will be noted that as destruction of the tubular tissue progresses in hypertensive disease, both kidneys behave in a similar manner, in that the blood flow per unit of tubular tissue is roughly equal in the two kidneys. In not a single instance is there any indication of significant unilateral ischemia.

In 6 of the subjects who were not operated on the tubular excretory mass was not measured; however, the fact that the rate of glomerular filtration and the effective renal blood flow were equally depressed in the two kidneys argues against the presence of unilateral ischemia.

The renal blood flow and the tubular excretory mass were found not to change significantly in 3 subjects when they were changed from a supine to an erect position, but change in position was not accompanied by an abnormal downward movement of the kidney, as determined by pyelography. In subject 16, however, the right kidney dropped when an erect position was assumed, the ureteropelvic junction remaining fixed, thereby producing an acute angulation of the ureter. With this ptosis was associated a reduction in the renal plasma flow from 225 to 110 cc., whereas it remained unchanged in the left kidney, 208 and 193 cc., respectively. With the subject in the upright position the tubular excretory mass measured in milligrams of iodine excreted per minute was 9.2 on the right side, as compared to 15.4 on the left side, giving values of 12.2 and 12.5 on the right and the left side, respectively, for the ratio of effective renal blood flow to tubular excretory mass. It appears that in this subject in the erect position each kidney received an equal amount of blood per unit of functioning tubular tissue. In view of this and the fact that the filtration fraction<sup>4</sup> remained the same regardless of position, it appears that reflex vasoconstriction of the afferent glomerular arterioles, elicited by the ptosis or by the presence of the catheter in the ureter, caused temporary occlusion of some of the tubular tissue in the right kidney when the subject changed position.

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4. By dividing the filtration rate (inulin clearance,  $C_{In}$ ) by the renal plasma flow ( $C_D$ ) the fraction of plasma filtered (filtration fraction) through the glomerulus can be determined.

*Pyelographic Data.*—The number of subjects examined is admittedly small, but it will be noted that they were selected at random. If unilateral renal ischemia is significant etiologically, we might expect in the group of 21 subjects to find some evidence of that fact. We have failed to do so. This negative result is particularly interesting in view of the circumstance that a number of these subjects had pyelograms, on one side or the other, which varied from the normal. Yet in spite of this fact the blood flow and the tubular excretory mass did not differ significantly on the two sides.

The pyelographic and the unilateral functional results have been recorded in the table. It will be seen that variations from the normal



Fig. 2 (subject 9).—*A*, retrograde pyelogram (supine position, anteroposterior view), showing angulation of the ureters and the low position of the right kidney. *B*, retrograde pyelogram (supine position, lateral view), showing tortuosity of the ureters.

pyelogram were present in 10 of the 21 subjects selected on the basis of hypertension alone. The variations ranged from simple low position or angulation of the ureter to ptosis and hydronephrosis. Low position of a kidney is generally accepted as having no significance; it occurred in 5 subjects, and in none was it associated with either hydronephrosis or a disturbance in renal function. Blunting of the calices, as seen in retrograde pyelography, can also be dismissed as having no significance unless the injection of the contrast medium is controlled as to pressure and volume. Of 5 normal subjects on whom retrograde pyelography was done, 2 showed dilatation of the ureters

and pelves apparently caused by abnormal injection, since these abnormalities were not present on second examination.

Angulation of the ureter was observed in 6 hypertensive subjects, in 2 the angulation being present on both sides. In all 6, however, the renal plasma flow per unit of functional tubular tissue was the same in the two kidneys.

Angulation of the ureter is frequently present without actual constriction of the lumen. In subject 9 (fig. 2 *A* and *B*) marked angulation appeared in the anteroposterior view; lateral views of the ureters



Fig. 3 (subject 14).—Retrograde pyelogram (erect position, anteroposterior view), showing angulation of the right ureter and ptosis and first degree hydronephrosis of the right kidney. The left kidney is normal

showed that they simply took tortuous courses without obstructive kinking. This tortuosity may account for apparent kinking in some instances in which on single anteroposterior examination the ureters have been reported as abnormal. Thompson and Bumpus<sup>5</sup> have demonstrated that acute angulations may be produced by deep inspiration, and they frequently observed a kink in one roentgenogram which was absent in a subsequent exposure (although the identical portion of the

5. Thompson, G. J., and Bumpus, H. C : Ureteral Kinks, *J. A. M. A* 94: 771-773 (March 15) 1930.

ureter was exposed) taken within a few minutes. Their explanation was that the kidney is displaced downward during deep inspiration and that the fixed point of the ureter where it leaves the peritoneum becomes the point of kinking.

It is apparent, therefore, that angulation of the ureters usually has little significance. When it is associated with hydronephrosis, it is generally assumed that the kinking has resulted in increased intrapelvic pressure and is responsible for this abnormality. In subject 14 (fig. 3) the pyelograms were interpreted as showing angulation of the ureter, ptosis and hydronephrosis (first degree) of the right kidney. Here, certainly, one must say that anatomically the right kidney is abnormal, and one might argue that the anatomic abnormality is the cause of the hypertension and on this basis recommend nephrectomy or nephropexy. Yet the renal blood flow to this abnormal right kidney was equal to that to the left kidney, 331 and 308 cc. per minute respectively. The tubular excretory mass was also the same on the two sides, indicating that at the present time the ptosed right kidney had not suffered injury in consequence of its ptosis. We must conclude that in this subject the hydronephrotic right kidney is merely coincidental and is not causally related to the elevated blood pressure. This subject had evidence, clinically, of long-standing hypertension, as indicated by enlargement of the heart, vascular changes in the ocular fundi and hemiplegia. Had the abnormal right kidney been responsible for the development of hypertension some time in the past and was the abnormal functional condition now present in the left kidney in turn the result of the hypertensive process, one might expect that the superimposition of hypertensive changes in the abnormal right kidney would have resulted in a continuation of the disparity of function on the two sides.

Not only did our pyelographic data fail to show a correlation with the functional status in these 24 hypertensive subjects, but in 1 of the 3 hypertensive subjects who had undergone surgical treatment a marked disparity in blood flow, filtration rate and tubular excretory mass in the two kidneys was associated with normal pyelograms.<sup>6</sup> Subject 22 (fig. 4) had lost more than 50 per cent of glomerular and tubular function; i.e., the left kidney was functionally only half as good as the right, and yet retrograde pyelography revealed kidneys appearing equal in size, with normal calices, pelves and ureters.

*Reliability of Specific Gravity of the Urine, Appearance Time of Dye and Intravenous Pyelography.*—If the rate of reabsorption of water by the tubules at a particular moment may vary in the two kidneys, theoretically one might expect a disparity in the concentration of total

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6. As urologists well know, retrograde, as compared to intravenous, pyelography throws little light on the functional status of the kidneys.

solids as well as in urine flow from kidneys of equal functional capacity. It will be noted that although the specific gravity is generally similar in the two kidneys, marked disparity does occur. Subjects 7 and 16 (table) exhibited significant variations, although the other functional measurements were in agreement. Inequality in urine flow is important in that it can readily lead to misinterpretation of the results of excretory tests of renal function; that is, the results of dye concentration tests may differ in the two kidneys, and yet their blood flow and



Fig. 4 (subject 22).—Retrograde pyelogram (supine position, anteroposterior view), showing no abnormalities in the size or the position of the kidneys; pelvis and ureters are normal.

functional capacity may be equal. In many instances, concentrations of phenolsulfonphthalein and diodrast in the urine were observed to vary considerably in kidneys with equal function, such variations always being related to urine flow, as is to be expected in theory. Moreover, since there is a large dead space in the ureters, pelvis and tubules, variations in the appearance time of the dye from two kidneys of equal functional capacity may also be the result simply of variations in rate of urine flow. The appearance time of the dye will vary inversely with

the urine flow. In subjects 11 and 14 (table) there was such prolongation of the appearance time on one side, although the other functional measurements were in agreement. This point is also significant in intravenous pyelography, since differences in concentrations of diodrast referable solely to differences in urine flow may result in differences in the roentgen shadow.

*Data on Three Hypertensive Subjects Surgically Treated for a Renal Condition.*—The 3 subjects remaining for discussion are dealt with together because they did not have uncomplicated hypertension but had undergone nephropexy, omentopexy or sympathectomy as therapeutic measures. The pyelographic and the functional data are given in the table.

B. F. was a 44 year old white woman with known hypertension of eight years' duration. In May 1939 she had had a bilateral splanchnicectomy performed in another hospital. Observations were made in June 1940, about one year later.

The effective plasma flow to the right kidney was 8 per cent lower than one-half the mean figure obtained in normal females, whereas that to the left kidney was 60 per cent lower. The tubular excretory mass was just about one-half the mean of the normal value in the right kidney, but one quarter of the mean normal value in the left kidney. Retrograde pyelograms in this subject were normal (fig. 4). Blood pressure levels were the same as those reported before operation.

This subject showed marked disparity in blood flow at a renal parenchyma in the two kidneys, but the blood flow per unit of tubular excretory mass was not significantly different in the two kidneys. Had excretory functional tests or even clearance determinations been done alone, the fact that the left kidney was receiving only one-half the amount of blood received by the right one might have been interpreted as indicating unilateral ischemia. However, since the tubular excretory mass was proportionately decreased in the left kidney, each unit of tubular excretory tissue received the same amount of blood as in the right kidney.

G. G. was a 17 year old girl with known hypertension of four years' duration. Left renal omentopexy was performed in June 1938, and unilateral observations were made in December 1939, eighteen months after operation.

The blood flow to the two kidneys before operation, determined on two occasions, was 818 and 830 cc. per minute; after operation the renal blood flow to the two kidneys was 689 and 691 cc. per minute, determined bilaterally and unilaterally, respectively. The blood flow to the kidney which was operated on was 36.6 per cent less, and in the kidney which was not operated on 16 per cent less, than one-half the mean figure obtained in normal females. Retrograde pyelograms were normal except for rotation of the surgically treated left kidney.

In this subject, then, the renal blood flow was lower in the kidney which was operated on than in the untreated one, and the total renal

blood flow was lower after operation. Blood pressure was unaffected by unilateral renal omentopexy.

L. J. was a 44 year old woman with known hypertension of four years' duration. Right nephropexy was performed in December 1938 for a ptosed kidney associated with costovertebral pain and hematuria. Unilateral observations were made in December 1940, two years later.

Retrograde pyelography revealed a normal left kidney, whereas the right kidney showed angulation of the ureter with first degree hydronephrosis. These pyelograms were compared with those taken before operation, and it was demonstrated that the operation had not changed the position of the kidney; although the angulation did not appear to be acute, there was increased dilation of the pelvis and blunting of the calices. Blood pressure levels were unchanged after operation.

The effective renal blood flow to the surgically treated right kidney and to the untreated left one was, respectively, 45 and 15.3 per cent less than one half the mean value obtained in normal female subjects. The tubular excretory mass was markedly decreased in both kidneys when compared to normal standards, but the blood flow per unit of tubular excretory mass was slightly below the normal figure on the treated side and definitely higher than this standard on the untreated side.

Since no unilateral preoperative data are available, and since surgical intervention failed to correct the anatomic deformity, we cannot draw any conclusion regarding the effect of nephropexy on the function of this kidney. Although the kidney which was operated on is receiving less blood per unit of functional tissue than the untreated one, the ratio of effective renal blood flow to tubular excretory mass is just 1 standard deviation below the mean normal value for the right kidney, and it is felt that neither kidney is ischemic.

#### CONCLUSIONS

The impairment of renal parenchyma in hypertensive subjects proceeds in a parallel manner in both kidneys, the pace varying in different persons. The decrease in renal blood flow is shared equally by the two kidneys. In 21 subjects with essential hypertension selected at random unilateral renal ischemia was not found to be present in a single instance.

Absolute reduction in blood flow to one or both kidneys, as measured by diodrast clearance, does not necessarily demonstrate that renal ischemia is present. This conclusion can be drawn only if the tubular excretory mass is measured, so that the blood flow per unit of tubular excretory tissue can be evaluated.

Many common variations in ureteropyelograms are believed to be without significance. Pyelographic abnormalities are not necessarily associated with functional disparity, and conversely, marked functional disparity may not be associated with pyelographic abnormalities.

The rate of reabsorption of water by the tubules and hence the rate of urine flow may vary markedly in two kidneys of equal functional



capacity. Excretory tests comparing the function of the two kidneys should therefore be evaluated with caution, for inequality in urine flow of itself can account for variations in specific gravity of the urine, in appearance time and relative concentration of dyes and in the roentgen shadows in excretory pyelography.

In 3 hypertensive subjects who had undergone surgical procedures for renal conditions significant disparities in the blood flow to the two kidneys were observed. In 1 subject who had undergone bilateral splachnicectomy the blood flow was less than normal in both kidneys and markedly so in one. In 2 subjects who had had unilateral operations (omentopexy and nephropexy) the blood flow to the treated kidney was less than that to the untreated kidney. In none of the 3 subjects did the elevated arterial tension fall after surgical therapy.

Drs. Arthur M. Wright, Samuel Standard and Howard S. Jeck performed the surgical procedures in this study, and Dr. Robert S. Hotchkiss read the ureteropyelograms.

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# MAINTENANCE OF NITROGEN EQUILIBRIUM BY INTRAVENOUS ADMINISTRATION OF AMINO ACIDS

## CLINICAL STUDIES

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In an earlier paper<sup>1</sup> it was shown that substitution of a mixture of essential amino acids for food protein is possible. A hydrolysate of casein reenforced by the addition of tryptophan was given subcutaneously or intravenously to normal persons and to patients after operation. Five of the 7 normal subjects stayed in nitrogen balance throughout the experiment. In the surgically treated subjects the injections helped to maintain nitrogen equilibrium.

Naturally, the question arose whether such injection of amino acids would be efficacious in the treatment of patients suffering from various disorders. In pursuit of this problem the following study was undertaken.

## MATERIAL AND METHOD

Nitrogen balance studies were made on 19 subjects observed over periods of two to thirteen weeks. There were 9 patients with malignant growths, 3 with hyperthyroidism, 1 with myxedema, 2 with empyema, 2 with chronic glomerulonephritis, 1 with cirrhosis of the liver and 1 with cardiac decompensation with icterus. The methods used were similar to those described previously.<sup>1</sup> The diet served was uniform through the alternating control and experimental periods. It varied from 50 to 60 calories and from 1.0 to 1.5 Gm. of protein per kilogram of body weight and was in general a high carbohydrate diet. The rejected

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1. Altshuler, S. S.; Hensel, H. M., and Sahyun, M.: *Am. J. M. Sc.* **200**:239, 1940.

food from each meal was returned to the diet kitchen, where it was weighed and its nitrogen content subtracted from that of the amount served.<sup>2</sup>

The mixture of amino acids used was the same as that described previously. It contained 1.0 per cent nitrogen, 5.0 per cent dextrose, 0.015 per cent potassium chloride, 0.7 per cent sodium chloride and traces of calcium and sulfate ions.<sup>3</sup> Before being used clinically each lot of amino acids was proved to be sterile and free from pyrogens. It was shown to be free of all reaction-producing substances when injected intravenously in daily increasing amounts of 1 to 300 cc. into at least 3 human subjects. Only lots entirely free from all such substances were used. When these precautions were taken, during the course of the study no reactions were encountered that could have been attributed to faulty material.

With the first lots used the rate of administration was about 0.3 Gm. of amino acid nitrogen per hour, but with improvement of the product the rate came to be 1 to 2 Gm. per hour. The criteria for determining the rate of administration were the subjective symptoms of the patient. When the rate of injection was too rapid the patient complained of flushing or burning of the skin, headache, backache, chills and fever and nausea, which in some cases progressed to vomiting. On decreasing the injection rate these symptoms rapidly subsided. It was also noticed that when the rate of administration was too rapid a greater percentage of the amino acids was excreted in the urine.

In all cases twenty-four hour specimens of urine were collected daily in clean dry jugs under toluene. Determinations of the total and the nonprotein nitrogen (by nesslerization<sup>4</sup>), amino acid nitrogen (by the method of Folin as modified by Sahyun<sup>5</sup>), creatine and creatinine<sup>4</sup> and urea nitrogen<sup>4</sup> were made daily. The nitrogen of the feces was not determined; however, in calculation 2 Gm. of nitrogen was added as an allowance for the feces. The amino acids administered were either excreted as such in the urine or retained in the body for metabolism. The amount excreted was calculated by subtracting the average daily urinary output of amino acid nitrogen during all the control periods from the average daily urinary output of amino acid nitrogen during each experimental period.

The amino acids retained in the body for metabolism were either deaminized or utilized for tissue protein synthesis. The quantity of amino acids deaminized was determined by subtracting the average daily excretion of urea nitrogen during all the control periods from the average daily excretion of urea nitrogen during each experimental period. No allowance has been made for daily variation in the food protein. Several formulas were tried to correct for this variation, but none was satisfactory. We acknowledge this limitation.

#### MALIGNANT GROWTHS

The first series of observations was made on patients with malignant growths. Because patients with carcinoma are subject to inanition and malnutrition they are poor surgical risks<sup>6</sup> and tolerate poorly high

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2. Waller, D.: Nutritive Value of Foods, University Hospital, Ann Arbor, Mich., unpublished data.

3. This material was prepared by Dr. Melville Sahyun, of Frederick Stearns and Company, Detroit.

4. Folin, O., and Wu, H.: *J. Biol. Chem.* **38**:81, 1919.

5. Sahyun, M., and Goodell, M.: *J. Lab. & Clin. Med.* **24**:548, 1939.

6. Ravdin, D. S.: *Ann. Surg.* **111**:915, 1940.

voltage roentgen therapy.<sup>7</sup> One prerequisite, then, for active treatment of carcinoma is that a patient be in a good state of nutrition.

Protein balance studies on patients with carcinoma have been conducted by various investigators. Von Mueller in 1886<sup>8</sup> and in 1889<sup>9</sup> made careful experiments on 9 patients with carcinoma and was able to reduce the loss of nitrogen by feeding a high caloric diet of 52 calories per kilogram of body weight, containing a total of 20.78 Gm. of protein nitrogen. Even so, the patients were not brought into positive nitrogen balance. Klemperer<sup>10</sup> in 1891 cited 8 patients with carcinoma, 3 of whom were fasting, while 5 had a low calory intake. Two of the fasting patients had a nitrogen output almost double the normal value; in the third the loss of nitrogen was within normal limits. Of the 5 remaining patients, 1 could be put into positive nitrogen balance by an increase of the caloric intake; the protein content of the diet was not mentioned. Wallersteiner<sup>11</sup> in 1914 investigated 20 cases of carcinoma in which the gastrointestinal tract was not involved, so that assimilation of food was normal. She selected cases in which there was extreme cachexia. She encountered a high output of nitrogen in only 10 per cent of the cases (2), and this nitrogen deficit was met by adequate high calory feedings. She interpreted this to mean that the high nitrogen output is probably due to extreme inanition only. Lauter and Jenke<sup>12</sup> in 1925 in experiments on minimal requirement of nitrogen found that in 2 of 3 cases of carcinoma there was an increased protein requirement of 70 and 100 per cent, respectively, above normal.

If one judges from the literature the consensus is that a patient with a malignant neoplasm could possibly be kept in nitrogen balance if the onset of inanition could be forestalled. It appeared that this might be effected by a high calory intake and the injection of amino acids. For this study patients were selected who were in a fairly good state of nutrition. Five of the 9 either were receiving or had recently received high voltage roentgen therapy.

The data obtained from studies of these 9 subjects with malignant neoplasms appear in table 1.

CASE 1.— A 54 year old man had a carcinoma of the floor of the mouth with extension into the mandibular bone; his ability to chew was moderately impaired. He was studied during three control and two experimental periods. During the first experimental period he retained 97.8 per cent of the amino acid nitrogen and during the second, 98.8 per cent. Although the food protein intake was less

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7. Nenda, P.: *Therap. d. Gegenw.* **65**:411, 1924.

8. von Mueller, F.: *Berl. klin. Wchnschr.* **41**:702, 1886.

9. von Mueller, F.: *Ztschr. f. klin. Med.* **16**:496, 1889.

10. Klemperer, G.: *Charité-Ann.* **16**:138, 1891.

11. Wallersteiner, E.: *Deutsches Arch. f. klin. Med.* **116**:145, 1914.

12. Lauter, S., and Jenke, M.: *Deutsches Arch. f. klin. Med.* **146**:323, 1925.

TABLE 1.—Results of Nitrogen Balance Studies on Patients with Malignant Neoplasms Given Amino Acids Intravenously

Case, Sex Age Yr.	Diagnosis	Roentgen Therapy	Weight, Kg.	Period *	Average Daily Intake of Nitrogen			Average Daily Output of Nitrogen					Average Daily Nitrogen Balance, Gm.
					Calories per Kg.	Protein Nitro- gen, Gm.	Amino Acid gen., Gm.	Total Nitro- gen, Gm.	Creati- nine gen., Gm.	Urea Nitro- gen, Gm.	Amino Acid gen., Gm.		
												Total Nitrogen, (Nonprotein Nitrogen, + 2 Gm. Feenl Nitrogen)	
1 ♂ 54	Carcinoma of the mouth	None	..... 65.90 63.18	C-2 AA-6 C-3	30.5 28.5 43.0	6.016 5.733 10.987	..... 9.667 .....	6.016 15.400 10.987	0.493 0.609 0.807	2.310 3.865 5.850	0.046 0.279 0.112	+0.938 +5.672 +1.227	
2 ♂ 52	Lymphosarcoma in the left tonsillar region	None	63.18 63.18 55.90 56.80	AA-7 C-7 AA-7 C-7	38.3 37.3 30.5 30.5	6.606 11.003 7.216 9.460	10.000 ..... 9.286 .....	16.606 11.003 16.502 9.460	0.426 0.325 0.580 0.725	2.807 1.734 4.920 2.704	0.265 0.051 0.272 0.077	+8.002 +6.112 +6.129 +0.610	
3 ♂ 62	Carcinoma of the colon	None	59.00 ..... 61.80	C-1 AA-7 C-7	18.7 16.0 21.0	3.128 5.437 6.306	..... 6.786 .....	3.128 12.223 6.306	0.750 0.480 0.407	3.200 3.080 2.164	0.061 0.240 0.065	-3.492 -2.917 +0.823	
4† ♀ 40	Multiple myeloma	None	65.50 ..... ..... .....	C-4 AA-5 C-5 AA-2	22.4 24.7 20.0 22.3	8.230 6.890 7.414 6.456	..... 4.000 7.414 6.850	8.230 10.890 7.414 11.306	0.615 0.634 0.692 0.232	5.088 3.856 2.393 1.167	0.070 0.148 0.044 0.051	-3.174 +1.055 -0.300 +6.201	
5 ♂ 57	Carcinoma of the bladder	4 doses of 200 r each	60.00 ..... ..... 58.6	C-6 AA-7 C-18 AA-5 C-2	30.0 35.0 27.0 3.052 11.0	11.020 8.475 7.912 8.000 4.216	..... 0.143 7.912 8.000 .....	11.020 14.618 7.912 10.292 4.216	0.469 0.808 0.431 0.189 0.172	0.808 4.297 1.986 2.424 2.450	0.228 0.469 0.131 0.205 0.051	+0.935 +0.098 -0.827 -0.760 -1.444	
6 ♂ 61	Carcinoma of the mandibula	8 weeks before study	61.00 60.45 59.00 55.0	C-2 AA-4 C-17 AA-17	24.5 34.0 31.0 29.8	6.378 7.739 7.663 5.991	..... 8.500 ..... 10.000	6.378 16.239 7.663 15.991	0.596 0.312 0.297 0.340	2.350 2.038 0.936 0.334	0.205 0.581 0.162 0.426	-1.089 +4.010 +0.309 +7.957	
7 ♂ 53	Carcinoma of the larynx and pulmonary tuberculosis	First course 37 days before study; second course started when study began	58.18 55.90 57.7	C-2 AA-7 C-8	42.0 49.0 45.0	13.728 13.909 14.116	..... 9.786 .....	13.728 23.765 14.116	0.633 0.735 0.605	5.220 5.174 4.669	0.105 0.587 0.113	+0.608 +8.764 +2.856	
8 ♂ 74	Carcinoma of the mouth and tongue	Just finished 30 daily treatments	43.6 42.4 ..... 43.5	C-3 AA-5 C-2 AA-4 C-7	29.0 27.0 38.0 41.9 36.0	5.951 1.982 5.916 2.548 6.325	..... 8.500 ..... 8.750 .....	5.951 10.482 5.916 11.293 6.325	0.374 0.527 0.416 0.557 0.543	0.957 2.516 2.018 4.400 2.094	0.061 0.568 0.079 0.501 0.113	-0.232 +0.594 +0.026 -0.665 +0.474	
9 ♂ 31	Lymphofibrosarcoma of the mesenterium and the mesenteric lymph nodes	12 daily doses of 200 r each before and 5 doses after outset of study	49.09 44.50	C-2 AA-7	23.0 24.0	4.096 3.534	..... 7.867	4.096 11.391	0.370 0.433	3.750 7.506	0.060 0.406	-4.019 -5.665	

\*The letter C designates a control period, and the letters AA, an experimental period. The numbers which follow these letters show the number of days in each period.

†The patient in case 4 had proteinuria; therefore figures for total nitrogen include 1.480 Gm. of urinary protein nitrogen during period a, 1.280 Gm. of urinary protein nitrogen during period b and 1.580 Gm. of urinary protein nitrogen during period c.

during the experimental periods, he retained a sufficient amount of amino acid nitrogen to increase the degree of positive nitrogen balance.

CASE 2.—A 52 year old man had a lymphosarcoma of the left tonsillar region with metastases to cervical and to submental lymph nodes. He was studied during one control and one experimental period. During the latter he retained 97.9 per cent of amino acid nitrogen, which was sufficient to increase the degree of positive nitrogen balance.

CASE 3.—A 62 year old man had a carcinoma of the descending colon; there was a partial intestinal obstruction, with carcinomatous peritonitis and ascites. The diagnosis was confirmed by biopsy of material taken at the time of laparoscopy. The patient was studied during two control and one experimental period. During the last-named period 97.4 per cent of the amino acid nitrogen was retained, which increased the positive nitrogen balance.

CASE 4.—A 46 year old woman had a multiple myeloma and a basal metabolic rate of +46 per cent. She was studied during two experimental and two control periods. During the first experimental period she was given 4.0 Gm. of amino acid nitrogen daily, of which 97.7 per cent was retained. This changed the negative nitrogen balance during the control period to a positive balance during this experimental period. During the second experimental period she was given 5.85 Gm. of amino acid nitrogen daily, all of which was retained.

CASE 5.—A 57 year old man had a carcinoma of the bladder with metastasis to the left femur. During the first control period he received four roentgen treatments of 200 r each to the left pelvic region as a palliative measure. The study included three control and two experimental periods. Although the food protein nitrogen intake decreased considerably during the experimental periods, a positive nitrogen balance was obtained, while the nitrogen balance was negative during the second and the third control period.

CASE 6.—A 64 year old man had a carcinoma of the right side of the mandibular bone. He had received a course of high voltage roentgen treatments from a private physician. The last treatment had been given about eight weeks before the start of this study. The investigation continued through two control and two experimental periods. During the first experimental period 95.2 per cent of the amino acid nitrogen was retained and during the second experimental period 97.6 per cent was retained. The patient was in negative nitrogen balance during the first control period but in positive balance during the other periods. The degree of positive balance was much higher during the experimental periods.

CASE 7.—A 53 year old man had a carcinoma of the larynx. A diagnosis of cavernous tuberculosis of the upper lobe of the right lung was made during the studies on nitrogen balance. He had a temperature up to 101 F. throughout. His legs were edematous. Serum protein values were 2.9 Gm. of albumin and 2.0 Gm. of globulin per hundred cubic centimeters. The edema was thought to be of nutritional origin, and injections of amino acids were suggested because one month of high protein, high vitamin diet and intramuscular injections of 3,000 international units of vitamin B<sub>1</sub> (thiamine hydrochloride) every second day did not correct the low serum protein values. The patient had finished the first course of roentgen therapy thirty-seven days before this study was begun, and a second course was started at the outset of the study. He was studied for three periods, two control and one experimental. During the last-named period the patient received 9.786 Gm. of amino acid nitrogen daily, of which 95.1 per cent was retained. This increased greatly the degree of positive balance. The blood

serum levels of albumin and globulin remained low. Hepatic function tests were done at the end of the study, including excretion of urobilinogen in the urine and the bromsulphalein, galactose and hippuric acid tests. The results of all tests were negative.

CASE 8.—A 74 year old man had a carcinoma of the floor of the mouth and the tongue; his ability to eat was much impaired. Before the beginning of this study he had received thirty daily irradiations of 200 r each. He was studied during three control and two experimental periods. During the final two periods his caloric and fluid intake were increased by additional injections of 2,000 cc. of 5 per cent dextrose solution daily. He was also given two blood transfusions of 500 cc. each during this time. In the first experimental period he received 8.5 Gm. of amino acid nitrogen daily, which was enough to convert the preceding negative balance into a positive one, even though less food protein was taken. During the second experimental period he received 8.75 Gm. of amino acid nitrogen daily, with which he did not maintain a positive nitrogen balance, partly because the urea nitrogen excretion was greatly increased. The results of hepatic function tests showed impairment.

CASE 9.—A 31 year old man had a lymphofibrosarcoma of the mesenterium and the mesenterial lymph nodes. At the outset of the study he received the last of twelve daily irradiations of 200 r each. He was given five more within the first week of the study. There were one control and one experimental period. During the latter he received 7.857 Gm. of amino acid nitrogen daily, of which 95.6 per cent was retained. The negative nitrogen balance in this patient also was in great part due to the marked increase of urea nitrogen excretion. Results of hepatic function tests were negative.

Data given in tables 1 and 4 show that in 7 of 9 patients suffering from malignant neoplastic diseases, nitrogen administered intravenously in the form of amino acid solution was almost completely utilized for the establishment or maintenance of a positive nitrogen balance.

In 7 patients the utilization of the amino acids injected was sufficient to convert a negative nitrogen balance to a positive one or to raise a positive one to a higher degree.

That high voltage roentgen therapy may have an effect on amino acid metabolism is suggested by the increase of urea nitrogen excretion in cases 8 and 9, causing a negative nitrogen balance in patients who had received roentgen treatments more recently than seven weeks before the beginning of the study.

Hepatic function tests were done on 3 patients, and the results revealed significant impairment in only 1 (case 8).

#### THYROID DISEASE

The next group investigated consisted of 3 patients with hyperthyroidism and 1 patient with myxedema (table 2).

CASE 10.—A 62 year old man had been under observation in the hospital for more than five months. After receiving 15 minims (0.92 cc.) of compound solution of iodine U. S. P. daily for four months the basal metabolic rate was reduced from  $+40$  to  $+4$  per cent. He was studied for one experimental and one control

TABLE 2.—Results of Nitrogen Balance Studies on Patients with Thyroid Disease Given Amino Acids Intravenously

Case Sex Age, Yr.	Diagnosis	Basal Metabolic Rate per Cent	Weight, Kg.	Period *	Average Daily Intake of Nitrogen				Average Daily Output of Nitrogen					Average Daily Nitrogen Balance, Gm.
					Calories per Kg.	Protein Nitrogen, Gm.	Amino Acid Nitrogen, Gm.	Total Nitrogen, Gm.	Total Nitrogen, Gm. (Nonprotein Nitrogen +2 Gm. fecal Nitrogen)	Creatinine Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino Acid Nitrogen, Gm.		
10	Hyperthy-	+ 4	40.2	AA-6	43.0	4.903	4.917	9.972	0.390	0.131	1.567	0.371	+0.439	
♂	roidism		41.8	C-6	44.0	4.440	.....	4.440	0.282	0.169	0.744	0.121	-1.087	
62														
11	Hyperthy-	+25	68.18	C-4	48.0	10.588	.....	10.588	0.852	0.131	5.963	0.092	-0.087	
♀	roidism		....	AA-6	58.5	12.924	4.583	17.507	0.823	0.129	7.202	0.359	+2.931	
19			71.0	C-7	57.5	13.607	.....	13.607	0.736	0.117	4.783	0.092	+3.376	
12	Hyperthy-	+63	62.5	C-4	80.7	16.617	.....	16.617	0.835	0.101	6.035	0.109	+5.637	
♂	roidism		....	AA-6	85.8	10.382	5.000	21.382	0.787	0.076	8.521	0.298	+5.753	
58			....	C-5	84.0	16.812	.....	16.812	0.760	0.061	5.981	0.105	+5.307	
13	Hypothy-	-40	60.0	C-3	10.5	4.336	.....	4.336	0.457	0.029	2.113	0.019	-1.600	
♀	roidism with		....	AA-6	21.7	4.966	4.000	8.966	0.371	0.057	2.089	0.111	+2.928	
71	myxedema		Desiccated thyroid started											
		-12	57.0	C-2	17.8	4.552	.....	4.552	0.518	0.239	1.665	0.029	-0.450	
		- 1	56.0	AA-6	22.1	4.708	3.917	8.625	0.302	0.095	2.001	0.102	+2.403	
		....	....	C-9	18.5	4.852	.....	4.852	0.240	0.078	1.261	0.033	-0.230	

\* The letter C designates a control period, and the letters AA, an experimental period. The numbers which follow these letters show the number of days in each period.



period, during both of which 1,000 cc. of 10 per cent dextrose solution was given intravenously daily in addition to the diet taken. During the experimental period he was given 4.917 Gm. of amino acid nitrogen daily, of which enough was retained to maintain a positive nitrogen balance, although the balance became negative in the succeeding control period. The patient gained 1.6 Kg. during the two periods.

CASE 11.—A 19 year old woman had had thyrotoxicosis for the past year, had been treated intermittently with compound solution of iodine and had received high voltage roentgen therapy five and a half months before the beginning of this study. The basal metabolic rate had been reduced to  $+25$  per cent. She was studied for three periods, two control and one experimental. During the last-named period she was given 4.583 Gm. of amino acid nitrogen daily, which changed the previously negative nitrogen balance to positive. Creatinine output was slightly above normal throughout the study.

CASE 12.—A 58 year old man had thyrotoxicosis, substernal thyroid enlargement and congestive heart failure with hypertrophy, dilatation and auricular fibrillation possibly of thyrotoxic origin. The congestive phenomena had disappeared before the onset of this study. The patient had received a course of high voltage roentgen therapy six weeks before the study was begun. The basal metabolic rate was  $+63$  per cent. He was studied for three periods, two control and one experimental. During the last-named period he was given 5.0 Gm. of amino acid nitrogen daily, 96.2 per cent of which was retained. The basal metabolic rate did not change during the study.

CASE 13.—A 71 year old woman had a history of myxedema of twenty years' duration without treatment. The basal metabolic rate was  $-40$  per cent. She was studied through three control and two experimental periods. Thyroid was given during the last experimental and the last two control periods. During the first experimental period, 4.0 Gm. of amino acid nitrogen was injected daily and the previous negative nitrogen balance was converted to positive. During the second experimental period, 3.917 Gm. of amino acid nitrogen was given daily, which again put the patient into positive nitrogen balance. Over 98 per cent of the amino acid was retained.

The patient with myxedema was in positive nitrogen balance with a much lower nitrogen and calory intake than were those with thyrotoxicosis. In the hyperthyroid patients a large percentage of the retained amino acids was deaminized. The patients in cases 10 and 11 gained weight, and the patient in case 12 improved clinically while under study; the patient in case 13 lost weight, probably because of the low caloric intake and the thyroid medication.

#### EMPHYEMA

Two patients with empyema showed a reversed serum albumin-globulin ratio; so both were given injections of amino acids (table 3). Both were constantly losing an undetermined amount of protein through the discharge of pus from their pleural incisions.

CASE 14.—A 59 year old man was studied during one experimental and one control period. During the former he was given 7.5 Gm. of amino acid nitrogen

TABLE 3.—Results of Nitrogen Balance Studies on Patients with Various Conditions Given Amino Acids Intravenously

Case Sex; Age, Yr.	Diagnosis	Weight, Kg.	Period *	Average Daily Intake of Nitrogen			Average Daily Output of Nitrogen								Average Daily Nitrogen Balance, Gm.
				Calories per Kg.	Protein Nitro- gen, Gm.	Amino Acid Nitro- gen, Gm.	Total Nitro- gen, Gm.	Total Nitrogen, Gm. (Nonprotein Nitrogen +2 Gm. Feenl Nitrogen)	Protein Urinary Nitrogen, Gm.	Non- protein Nitrogen, Gm.	Creati- nine Nitrogen, Gm.	Creatine Nitrogen, Gm.	Urea Nitrogen, Gm.	Amino Acid Nitrogen, Gm.	
14	Empyema in right pleura	60.9	AA— 6	21.2	5.472	7.500	12.972	13.295	.....	11.295	0.296	0.143	.....	0.491	—0.323
59	♂	61.36	C— 7	21.1	7.657	.....	7.657	9.541	.....	7.514	0.502	0.128	.....	0.143	—1.887
15	Empyema in left pleura	45.0	AA— 6	39.3	7.965	7.417	15.382	10.309	.....	8.309	0.321	0.128	.....	0.337	+5.073
66	♂	....	C— 7	37.2	10.032	.....	10.032	8.883	.....	6.883	0.218	0.185	.....	0.107	+1.149
16	Chronic nephritis	61.4	AA— 9	38.7	8.480	4.100	12.880	6.399	0.902	3.497	0.739	0.096	.....	0.158	+6.481
54	♂	63.4	C —7	40.7	9.650	.....	9.650	3.972	0.797	1.175	0.485	0.070	.....	0.039	+5.678
17	Chronic glomerulo- nephritis with edema	62.7	C— 6	41.4	12.230	.....	12.230	13.961	1.487	10.177	0.968	0.096	5.691	0.073	—1.731
29	♀	61.36	AA— 5	40.3	10.866	7.200	18.066	11.821	0.726	9.093	0.729	0.013	5.313	0.230	+6.245
		60.0	C— 4	36.5	10.473	.....	10.473	8.398	0.451	5.947	0.569	0.068	3.717	0.039	+2.075
		60.0	AA— 8	31.7	8.394	5.525	13.919	13.291	0.597	10.697	0.880	0.095	6.267	0.241	+0.625
		63.6	C—16	28.0	11.181	.....	11.181	9.814	0.208	6.906	0.808	0.031	4.291	0.042	+1.367
		60.00	AA— 5	33.5	10.186	7.170	17.356	12.679	0.471	10.208	0.913	0.066	6.375	0.219	+4.677
		63.6	C— 7	32.4	11.910	.....	11.940	14.900	1.785	11.115	1.168	0.073	6.285	0.018	—2.960
		62.5	AA— 6	33.0	11.080	4.500	15.580	14.645	1.747	10.898	1.098	0.062	6.058	0.242	+0.935
		61.3	C— 7	31.1	12.480	.....	12.480	12.183	1.973	8.210	1.159	0.065	3.952	0.070	+0.297
18	Cirrhosis of the liver	87.7	AA—15	23.6	11.350	5.000	16.350	17.148	1.226	13.922	1.151	0.156	.....	0.320	—0.798
45	♂	84.8	C— 7	21.0	6.560	.....	6.560	9.390	2.098	5.292	0.487	0.104	.....	0.077	—2.830
19†	Cardiac insuffi- ciency; tetanus; ascites	81.3	C— 5	24.6	10.675a	.....	12.723	7.351	.....	5.351	0.301	0.051	.....	0.075	+5.372
57	♂	....	AA— 4	16.3	5.390b	5.250	12.120	11.125	.....	9.125	0.289	0.135	.....	0.231	+0.995

\*The letter *C* designates a control period, and the letters *AA*, an experimental period. The numbers which follow these letters show the number of days in each period.

†The patient in case 19 received 2.048 Gm. ammonium nitrate nitrogen during the period marked *a* and 1.195 Gm. during the period marked *b*. Both amounts are included in the total nitrogen intake.

daily, of which 95.4 per cent was retained to decrease the negative nitrogen balance. The values for serum albumin and globulin did not change.

CASE 15.—A 66 year old man was studied for one experimental and one control period. During the former he was given 7.417 Gm. of amino acid nitrogen daily, which resulted in a positive nitrogen balance 3.9 Gm. daily higher than that of the control period.

It was not possible to determine the urinary excretion of urea nitrogen in cases 14 and 15, so the utilization of amino acid nitrogen could not be accurately calculated; however, the effect of the injections on the nitrogen balance was favorable.

#### NEPHRITIS

Two patients had conditions given the diagnosis of chronic glomerulonephritis (table 3).

CASE 16.—A 54 year old man had been admitted to the hospital in a pre-uremic condition and was considered to be in an azotemic state of chronic glomerulonephritis. Six weeks after admission, when the emergency had subsided and the nonprotein nitrogen was down to 48 mg. per hundred cubic centimeters, this study was started. The patient was observed through one experimental and one control period. Serum albumin and globulin were low. He received supplements of vitamin B<sub>1</sub> and riboflavin and 0.5 grain (0.03 Gm.) of desiccated thyroid daily. He had received injections of mercupurin before the study began, and for this reason urea nitrogen determinations were not done. During the experimental period of nine days the patient received 4.4 Gm. of amino acid nitrogen daily, of which 97.3 per cent was retained. The patient gained 2 Kg. in weight, which, however, may have been due to increased tissue edema. The nitrogen balance was made more positive.

CASE 17.—A 29 year old woman had a condition given the clinical diagnosis of chronic glomerulonephritis with secondary hypertension, anemia and edema. With a nitrogen intake of 12.23 Gm. daily the patient was in negative nitrogen balance, losing 1.734 Gm. daily. The output of creatine was in the upper limits of normal at 96 mg. per hundred cubic centimeters. There were five control and four experimental periods. During the last-named periods she received an average of 6.1 Gm. of amino acid nitrogen daily, of which about 97 per cent was retained. The serum albumin at the start of the study was 1.52 Gm. per hundred cubic centimeters, and at the end it was 2.3 Gm. The serum globulin at the time of the third control period was 2.9 Gm. per hundred cubic centimeters and at the end of the study 5.2 Gm. It can be surmised that the regeneration of the plasma protein was due to the amino acids.

Both of these patients had hypoproteinemia, and both retained a significant amount of amino acids for protein synthesis. In these patients the injections maintained or increased positive nitrogen balances. These results confirm those of Farr and co-workers.<sup>13</sup>

13. Farr, L. E., and MacFadyen, D. A.: *Proc. Soc. Exper. Biol. & Med.* **42**:144, 1939. Farr, L. E.; Emerson, K., and Fulcher, P. H.: *J. Pediat.* **17**:595, 1940.

## HEPATIC DISTURBANCES (TABLE 3)

CASE 18.—A 45 year old man had cirrhosis of the liver, with splenomegaly and ascites, and a history of chronic alcoholism of twenty years' duration. Supplements of vitamin B complex and vitamin C, as well as injections of dextrose were given during the study. The serum contained 1.8 Gm. of albumin and 5.2 Gm. of globulin per hundred cubic centimeters. The administration of mercupurin made data on urea nitrogen excretion unreliable. The patient was studied through one control and one experimental period. During the latter, which lasted fifteen days, 5.0 Gm. of amino acid nitrogen was given daily, of which 95.2 per cent was retained. The negative nitrogen balance was about 2.0 Gm. less during the experimental period than during the following control period. This may in part be explained by the decrease of food protein intake during the control period. The blood albumin-globulin ratio was not changed. The icteric index was 31, and abnormal results of three hepatic function tests showed decreased function.

CASE 19.—A 57 year old man was admitted in an acute state of cardiac insufficiency with icterus, ascites and edema. He was studied for one control and one experimental period, during which time he was receiving 3,000 international units of vitamin B<sub>1</sub> (thiamine hydrochloride) intramuscularly and ammonium nitrate in amounts equaling 2.048 Gm. of nitrogen daily. During the experimental period he was given 5.25 Gm. of amino acid nitrogen daily, but a decrease in food protein neutralized the effect produced by these injections, so that the total intake was about the same in these two periods. However, 96 per cent of the amino acid administered was retained.

Although these 2 patients with hepatic disturbances retained about 95 per cent of the amino acid administered, there was no apparent improvement in the nitrogen balance.

## COMMENT

The results of the nitrogen balance studies on 19 patients who received a solution of amino acids intravenously are shown in tables 1, 2 and 3. The figures are average daily determinations throughout the periods of study. In changing from a control to an experimental period the reflection in the nitrogen excretion, or the "lag," from one regimen to the other was a matter of hours rather than days, and consequently it was not considered necessary to put the patients on preparatory regimens between periods.

It was observed that in some instances in which there were two or more control periods, during the control period following an experimental period there was a lower nitrogen deficit or a greater positive balance. An example is seen in case 11. This was not interpreted to be a lag of protein metabolism holding over from the experimental period but rather to indicate that a patient was better able to utilize the nitrogen of his food. This may represent a beneficial effect on the mechanism of protein metabolism. However, on this point further investigation is needed.

The fate of the amino acids utilized in the body is, first, the replacement of body protein which is broken down by catabolism and, second;

utilization for some specific purpose, such as formation of hormones, bile salts, catalysts, purines, pigments, etc. However, if the intake of carbohydrates and fat is inadequate for caloric needs, body protein may be broken down to be used for energy. Under such circumstances the amino acids might be burned directly or converted into sugar and fat. Inasmuch as no other substance can be substituted for the essential

TABLE 4.—Disposition of Amino Acids Intravenously Administered to Patients with Various Disorders

Case	Amino Acid Nitrogen Given, Gm.	Amino Acid Nitrogen Utilized						
		Amino Acid Nitrogen Excreted*		Percentage of Total	Nitrogen from Deamination †		Protein Synthesis	
		Gm.	Per Cent		Gm.	Per Cent	Gm.	Per Cent
1	9.667	0.208	2.2	97.8	0.567	5.9	8.892	91.9
	10.000	0.197	1.2	98.8	—0.491‡	...	9.802	98.8
2	9.286	0.194	2.1	97.9	2.216	23.9	7.875	74.0
3	6.786	0.176	2.6	97.4	0.998	14.7	5.611	82.7
4	4.000	0.091	2.3	97.7	1.193	29.8	2.716	67.9
	5.850	0.000	0.0	100.0	—1.126‡	...	5.850	100.0
5	6.143	0.320	5.2	94.8	2.522	41.1	3.800	63.7
	8.000	0.067	0.8	99.2	0.649	8.1	7.283	91.1
6	8.500	0.407	4.8	95.2	0.395	4.6	7.698	90.6
	10.000	0.242	2.4	97.6	—1.309‡	...	9.758	97.6
7	9.786	0.478	4.9	95.1	0.230	2.3	9.078	92.8
8	8.500	0.483	5.7	94.3	0.817	9.6	7.299	84.7
	8.750	0.416	4.7	95.3	2.801	32.0	5.532	63.3
9	7.857	0.349	4.4	95.6	3.756	47.8	3.752	47.8
10	4.917	0.247	5.0	95.0	0.823	16.7	3.847	78.3
11	4.583	0.266	5.8	94.2	1.829	39.9	2.487	54.3
12	5.000	0.190	3.8	96.2	2.516	50.3	2.293	45.9
13	4.000	0.002	1.5	98.5	0.407	10.2	3.531	88.3
	3.917	0.070	1.8	98.2	0.322	8.2	3.524	90.0
17	7.200	0.176	2.4	97.6	0.526	7.3	6.498	90.3
	5.525	0.186	3.4	96.6	1.480	26.7	3.858	69.9
	7.170	0.165	2.3	97.7	1.588	22.1	5.417	75.6
	4.500	0.184	4.0	96.0	1.271	28.2	3.045	67.8

Case	Amino Acid Nitrogen Given, Gm.	Amino Acid Nitrogen Excreted *		Amino Acid Nitrogen Utilized	
		Gm.	Per Cent	Gm.	Per Cent
14	7.500	0.348	4.6	7.152	95.4
15	7.417	0.230	3.1	7.187	96.9
16	4.400	0.120	2.7	4.281	97.3
18	5.000	0.242	4.8	4.758	95.2
19	5.250	0.206	3.9	5.043	96.1

\* Amino acid nitrogen excreted in the urine in excess of that excreted during the control period(s).

† Amino acid nitrogen from deamination is the amount of increase in the urea nitrogen excreted over that excreted during the control period(s).

‡ See the text for the explanation of decreased deamination.

amino acids to build body protein, it is of some importance to determine how much of the amino acids administered in this study was retained for the purpose of anabolism.

Table 4 shows the amount of the amino acids excreted, the amount deaminized and the amount retained and presumably used for building body proteins. These amounts are expressed both absolutely and relatively. The amount excreted is determined by subtracting the average amount of amino acid nitrogen excreted in the urine during the control

periods from the amount excreted during each of the experimental periods. The amount deaminized is determined by subtracting the average amount of urea nitrogen excreted in the urine during the control periods from that excreted during each experimental period. We recognize that these estimated values are only approximations. The sum of the amount of amino acid nitrogen excreted and the amount deaminized subtracted from the total amino acid nitrogen administered gives the amount retained and presumably utilized for body proteins.

In cases 1, 4 and 6 experimental periods occurred in which the excretion of urea nitrogen was less than that during the control period. It is suggested that this may indicate a protein-sparing action of the amino acids.

The patients with malignant neoplasms retained between 94.3 and 100.0 per cent of the amino acids, of which 47 to 100 per cent was used presumably for protein synthesis.

In the patients with hyperthyroidism (cases 10, 11 and 12) the amino acid retention was about 95 per cent, of which 78.3 per cent, 54.3 per cent and 45.9 per cent, respectively, was used presumably for protein synthesis.

The patient with hypothyroidism and myxedema (case 13) retained over 98 per cent of the amino acids administered, of which almost 90 per cent was used for protein synthesis.

The patients with empyema (cases 14 and 15), as well as those with chronic nephritis (cases 16 and 17), retained almost all of the amino acids administered. Both of the latter patients had hypoproteinemia at the beginning of the study. The amino acids were also well utilized by the patients with hepatic disturbances (cases 18 and 19). However, because determinations of urea nitrogen were not made on 5 of these last 6 patients, it is not possible to establish how much of the amino acids metabolized was used for protein synthesis.

Referring again to the first three tables, the data on creatine and creatinine are difficult to interpret because the figures are so widely divergent. Normally, men excrete insignificant amounts of creatine, though in children and to some extent in women the excretion of moderate amounts of the substance is physiologic.<sup>14</sup> Creatine and creatinine metabolism is regarded as a phase of endogenous protein metabolism, and the amount of creatinine excreted, a measure of this metabolism.<sup>14</sup> The excretion of creatinine is thought to be uninfluenced by protein in the diet.<sup>14</sup> However, it has been pointed out that a large number of factors enter into this matter. Creatinuria is manifested in starvation, muscular diseases, exophthalmic goiter, eclampsia and dia-

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14. Bodansky, M.: *Introduction to Physiological Chemistry*, New York, John Wiley & Sons, 1934, p. 429.

betes.<sup>15</sup> All forms of creatinuria are due either to incomplete storage of creatine or to the incomplete conversion of creatine to creatinine, so that the amount of creatine present in the urine is at the expense of creatinine.<sup>14</sup> Beard<sup>16</sup> expressed the opinion that any amino acid except proline or oxyprolin if fed or injected in sufficient amounts will increase creatine formation and excretion. This concept is not universally accepted.<sup>17</sup>

Because the total amount of creatine and creatinine in tissue and in urine is independent of the diet, the interpretation of the data is difficult. There was considerable variation in creatine excretion and creatinine excretion in the same patient. With this qualification the following phenomena were observed: The patient with multiple myeloma (case 4) excreted about three times the normal amount of creatine; the patient with lymphofibrosarcoma (case 9), about four times the normal amount, and 1 patient with carcinoma of the mouth (case 8), twice the normal amount. The 3 patients with hyperthyroidism (cases 10, 11 and 12) excreted an amount greater than the normal, while the patient with myxedema (case 13) excreted less than normal. The 2 patients with infections (cases 14 and 15) and 1 of the patients with cirrhosis (case 18) also had high creatine and creatinine excretions.

#### CONCLUSIONS AND SUMMARY

Solutions of amino acids can be administered intravenously at the rate of 1 to 2 Gm. of amino acid nitrogen per hour.

Solutions of amino acids injected into 19 patients suffering from various diseases were uniformly well tolerated.

Over 94 per cent of the amino acids administered intravenously was utilized in 9 patients with malignant neoplasms, 3 patients with hyperthyroidism, 1 patient with hypothyroidism, 2 patients with chronic infections, 2 patients with chronic nephritis and 2 patients with cirrhosis of the liver.

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15. Bodansky, M., and Bodansky, O.: *Biochemistry of Disease*, New York, The Macmillan Company, 1940, p. 417.

16. Beard, H. H., in Luck, J. M.: *Annual Review of Biochemistry*, Stanford University, Calif., Annual Reviews, Inc., 1941, p. 245.

17. Schoenheimer, R., and Ratner, S., in Luck, J. M.: *Annual Review of Biochemistry*, Stanford University, Calif., Annual Reviews, Inc., 1941, p. 213.

# PRODUCTION AND STUDY OF CARDIAC FAILURE IN THIAMINE-DEFICIENT PIGEONS

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Although cardiac failure occurs frequently in thiamine-deficient human beings (beriberi<sup>1</sup>), it is rarely encountered in animals with experimental thiamine deficiency. MacCarrison<sup>2</sup> and Findlay<sup>3</sup> observed hydropericardium in an occasional pigeon allowed to eat a thiamine-deficient ration ad libitum. Other indications of cardiac failure were lacking, however, and these experiments were done so early that it was impossible to exclude other contributing nutritional causes. More recently, signs and symptoms of cardiac failure have been produced in thiamine-deficient dogs.<sup>4</sup> Bradycardia has been noted in thiamine-deficient pigeons,<sup>5</sup> with and without abnormal electrocardiograms, whereas

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1. (a) Kepler, E. J.: Beriberi from a Diet of Raw Starch, *J. A. M. A.* **85**: 409 (Aug. 8) 1925. (b) Scott, L. C., and Herrmann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana, *ibid.* **90**:2083 (June 30) 1928. (c) Keefer, C. S.: The Beriberi Heart, *Arch. Int. Med.* **45**:1 (Jan.) 1930. (d) Inada, R.: Symptoms and Pathological Aspects of the Disturbances of the Circulatory System in Beriberi, in *Contributions to Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 2, p. 577. (e) Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, *Tr. A. Am. Physicians* **51**:341, 1936. (f) Vedder, E. B.: Beriberi and Vitamin B<sub>1</sub> Deficiency, *Am. J. Trop. Med.* **20**:625, 1940. (g) Tice, F.: *Practice of Medicine*, Hagerstown, Md., W. F. Prior Company, Inc., 1920.

2. MacCarrison, R.: The Pathogenesis of Deficiency Disease, *Indian J. M. Research* **6**:225, 1919.

3. Findlay, G. M.: An Experimental Study of Avian Beriberi, *J. Path. & Bact.* **24**:175, 1921.

4. Swank, R. L.; Porter, R., and Yeomans, A.: The Production and Study of Cardiac Failure in Thiamin Deficient Dogs, *Am. Heart J.* **22**:154, 1941.

5. Carter, C. W., and Drury, A. N.: Heart Block in Rice Fed Pigeons, *J. Physiol.* **68**:i, 1929. Carter, C. W.: Heart Block in Pigeons: Curative Factor, *Biochem. J.* **24**:1811, 1930; Maintenance Nutrition in the Pigeon and Its Relation to Heart Block, *ibid.* **28**:932, 1934. Méhes, J., and Péter, F.: Die Wirkung des Digitoxins auf das E.K.G. der normalen und der an experimenteller Beriberi erkrankten Tauben, *Arch. f. exper. Path. u. Pharmakol.* **176**:226, 1934.



tachycardia has been observed in thiamine-deficient dogs.<sup>6</sup> In rats bradycardia has been observed by some investigators,<sup>7</sup> but others<sup>8</sup> have expressed the opinion that this might be due to concomitant starvation.

In a recent paper<sup>9</sup> we have pointed out that the symptoms of experimental thiamine-deficiency in pigeons vary greatly depending on the form of the deficiency. In pigeons that are made acutely deficient in thiamine by tube feeding, so that fasting is prevented, opisthotonos develops. When, however, they are made chronically deficient (depleted of thiamine slowly by feeding them by tube a diet but partially free of thiamine), ataxia and later weakness of the legs develop. Many chronically deficient pigeons, but none of the acutely deficient ones, were found at autopsy to have incidental evidence of a failing heart, such as hydropericardium, pulmonary congestion and edema, engorgement of the liver and (or) edema of dependent parts, and if their already low thiamine intake was discontinued a few days before autopsy, acute cardiac failure, with dyspnea at rest, developed. Areas of necrosis in the myocardium with polymorphonuclear cell infiltration and histologic confirmation of pulmonary congestion were observed in many of these pigeons.<sup>10</sup>

In this paper the results of clinical, pathologic, chemical and electrocardiographic studies on pigeons that exhibited changes compatible with cardiac failure will be reported in greater detail.<sup>10a</sup>

#### MATERIAL AND METHOD

All of the observations were made on white Karneaux pigeons 6 to 8 weeks old at the beginning of experimentation. They were fed by tube and caged as

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6. de Soldati, L.: Los trastornos circulatorios del perro en avitaminosis B<sub>1</sub>. El pulso, la tension arterial y el electrocardiograma, *Rev. Soc. argent. de biol.* **15**:142, 1939. Swank, Porter and Yeomans.<sup>4</sup>

7. (a) Drury, A. N.; Harris, L. J., and Maudsley, C.: Vitamin B deficiency in the Rat: Bradycardia as a Distinctive Feature, *Biochem. J.* **24**:1632, 1930. (b) Birch, T. W., and Harris, L. J.: Bradycardia in the Vitamin B<sub>1</sub> Deficient Rat and Its Use in Vitamin B<sub>1</sub> Determinations, *ibid.* **28**:602, 1934. (c) Weiss, S.; Haynes, F. W., and Zoll, P. M.: Electrocardiographic Manifestations and the Cardiac Effect of Drugs in Vitamin B<sub>1</sub> Deficiency in Rats, *Am. Heart J.* **15**:206, 1938. (d) Baker, A. Z., and Wright, M. D.: A Survey of the Rat Bradycardia Method of Estimating Vitamin B<sub>1</sub>, *Biochem. J.* **39**:1370, 1939.

8. Parade, G. W.: Vitamin B-Untersuchungen. Zur Frage des Zusammenhanges zwischen Vitamin B<sub>1</sub>-Mangel und Bradykardie, *Ztschr. f. Vitaminforsch.* **6**:327, 1938; Vitamin B<sub>1</sub> Mangel, Bradykardie und Temperatursturz, *ibid.* **7**:35, 1938. MacDonald, D. G. H. and McHenry, E. W.: Studies on Rat Bradycardia, *Am. J. Physiol.* **128**:608, 1940.

9. Swank, R. L., and Bessey, O. A.: Avian Vitamin B<sub>1</sub> Deficiency: Characteristic Symptoms and Their Pathogenesis, *J. Nutrition* **22**:77, 1941.

10. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, *J. Exper. Med.* **71**:683, 1940.

10a. Dr. C. Sidney Burwell contributed helpful suggestions.

described in another paper.<sup>9</sup> Most of the birds received a purified thiamine-free diet (diet II) containing 20 per cent casein (alcohol extracted), 65 per cent corn starch, 4 per cent cod liver oil, 5 per cent peanut oil, 4 per cent salt mixture and vitamin K concentrate. Acute deficiency and death was produced by this method in about two weeks. Chronic deficiencies of various degrees of severity were produced as described by the addition to the diet of variable but inadequate daily doses of thiamine hydrochloride. Autoclaved yeast (the usual source of other members of the vitamin B complex) was not included in this diet because it always contains an unknown and variable amount of thiamine and because with autoclaved yeast absent from the diet it was possible to attribute curative responses to the thiamine alone. Other control birds received this diet plus 15 per cent autoclaved yeast (diet III) but will not be described separately, as their behavior was not significantly altered by this dietary improvement. No birds received diet II for longer than six weeks, for, as pointed out previously,<sup>9</sup> apparent normal nutrition is not supported by this diet for longer than eight to twelve weeks because of the absence of other factors, both known and unknown, which are nutritional essentials for pigeons.

Conventional three lead electrocardiograms were made at regular intervals with a cardiette type of apparatus. The feathers were plucked from the bases of both wings and from the left leg. Electrode paste was rubbed into the skin and spring brass clamps fastened to the skin. Leading from these clamps were insulated copper wires 18 inches (46 cm.) long, with spring snaps at their free ends. These snaps could be connected to the leads of the electrocardiographic apparatus at any time without disturbing the pigeon to which the brass electrodes were connected. After the electrodes had been applied, the bird was secured in a pigeon holder (see description in another paper<sup>9</sup>) which was supported at an angle of about 55 degrees. Six pigeons at a time were made ready in this manner and allowed to rest for ten to fifteen minutes in the dark. The spring snaps attached to the copper wire leads were then clamped to the proper electrocardiographic leads and the records made quickly without disturbing the animals. In many other preliminary experiments the cardiac rate was counted directly by auscultating the breast with a small bell stethoscope.

The hearts of many of the birds that were killed were studied histologically, and in many instances the cocarboxylase (thiamine pyrophosphate) activity of the cardiac musculature was determined. In other birds the electrical activity of the cardiac musculature was studied after an intravenous injection of thiamine hydrochloride or cocarboxylase.

#### OBSERVATIONS

*Clinical and Pathologic.*—In preliminary experiments the cardiac rates of many normal pigeons and of 80 or more birds made acutely or chronically deficient according to the tube feeding method just outlined were determined directly twice each week. Few of the animals lost more than 10 per cent of their original weight, and many gained weight during the experiments. Normally, the cardiac rate varied between 150 to 250 contractions per minute, which agrees essentially with data compiled by Buchanan.<sup>11</sup> Significant slowing of the rate was

11. Buchanan, F.: The Frequency of the Heart Beat and the Form of the Electrocardiogram in Birds, *J. Physiol.* **38**:lxii, 1909.

not noted consistently either in the acutely or in the chronically thiamine-deficient animals that were fed by tube. However, marked decreases in the cardiac rate were observed in control fasting animals that were allowed to lose 25 to 35 per cent of their weight in twenty to thirty days while consuming small rations of mixed grain plus 50 micrograms of thiamine hydrochloride daily. In these pigeons cardiac rates of 75 to 100 per minute were frequent, and in several instances rates between 50 and 75 were noted. In most fasting animals the cardiac rhythm was irregular.

The hearts of the fasting and of the acutely deficient pigeons were histologically normal. However, many hearts from chronically deficient pigeons with evidences of cardiac failure revealed unquestionable degeneration. The earlier changes consisted of a loss of cross striations and development of a wavy fibrous appearance and pale staining reactions of the muscle fibers; the later ones consisted of necrosis of muscle fibers with polymorphonuclear cell infiltration.

*Electrocardiographic Studies.*—Twenty-three birds were used for these experiments. All except the normal controls, which consumed mixed grain, were fed by tube. This expedient prevented a greater than 8 per cent loss of weight in all but 2 birds and produced a slight gain in weight in 4 pigeons. Six pigeons were fed 20 Gm. of diet daily until they vomited and then 15 Gm. and no thiamine; they became deficient acutely and had opisthotonos. The remaining pigeons were given 20 Gm. of diet until they vomited, on about the eighth day. The daily diet was then reduced to 15 Gm. and was supplemented by 15 micrograms of thiamine hydrochloride daily. On the fourteenth experimental day the thiamine hydrochloride intake of 5 pigeons was further reduced to 10 micrograms daily, and six days later the remaining 12 birds were treated similarly. These pigeons were thus depleted of thiamine slowly, and the symptoms characteristic of chronic deficiency developed, as described previously.<sup>12</sup>

Control electrocardiographic records were made on each pigeon on the first and the third or on the second and the fourth day of an experiment. Subsequent single studies were repeated when the birds vomited (on about the eighth day), and daily studies were made on the acutely deficient birds before, during and after opisthotonos developed and on the chronically deficient pigeons after the thiamine hydrochloride intake was reduced to 10 micrograms daily. Other special studies were made and will be described.

*General Appearance of the Normal and of the Control Electrocardiograms:* The general appearance of both types of electrocardiogram

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12. Swank and Bessey.<sup>9</sup> Swank.<sup>10</sup>

was uniform (fig. 1 *A*, *B* and *C*). The P waves in all leads were upright and about 2 mm. high. The P-QRS interval averaged eight hundredths of a second in duration (four hundredths of a second or less when the rate was fast and as long as twelve hundredths of a second when the rate was slow). It was followed by the QRS complex, the first and main deflection of which was directed downward in all leads, for a distance of 1 to 3 mm. in the first, and 8 to 12 mm. in the second and the third, lead. This complex lasted two to three hundredths of a second and became continuous with the upright T wave, which was barely discernible in lead I and prominent in leads II and III. In normal resting birds the ventricular rate varied from 150 to 250 per minute.

**Types of Abnormal Electrocardiograms and Their Occurrence:** During the period of vomiting between the seventh and the ninth day of the experiment, a slight, and in many instances definite, slowing of the heart rate occurred. In a few instances this was attended by variable heart block (fig. 1 *D*, *E* and *F*), during which the P-QRS interval (when the QRS wave was present) was long and variable (ten to sixteen hundredths of a second).

With the development of symptoms of thiamine deficiency the electrocardiograms of 2 of the 6 acutely deficient pigeons with opisthotonos and of all but 1 of the chronically deficient pigeons with or without weakness of the legs exhibited significant alterations, usually in the T waves of leads II and III and occasionally in the QRS complexes of leads I and II. In others, a combination of these changes occurred.

In figure 1 *G*, *H* and *I* the most commonly observed type of electrocardiographic change is illustrated. There is no significant change in lead I (figure 1 *G*). In lead II (figure 1 *H*) and lead III (figure 1 *I*), the T waves are inverted and the initial deflections of the QRS complexes are directed upward for 1 to 2 mm. Figure 1 *J*, *K* and *L* illustrate a much less frequently observed type of change. The QRS complex in lead I is large and directed upward (inverted) and in lead II is biphasic with its main deflection upward. In lead III the QRS complex appears normal but for a small initial deflection which is upward. The P waves are prominent in leads I and II and small in lead III, and the T waves are unaffected.

One electrocardiogram obtained on a severely deficient pigeon just before death recorded rapid and irregular ventricular deflections followed by ventricular asystole (figure 1 *M*, lead I).

**Ventricular Rate:** During the first four experimental days the cardiac rate in birds at rest varied between 150 and 250 per minute, the same as was observed in other, normal birds. When vomiting first occurred, on the seventh to the ninth day, there was a definite tendency toward bradycardia (20 to 50 per cent reduction in cardiac rate) in

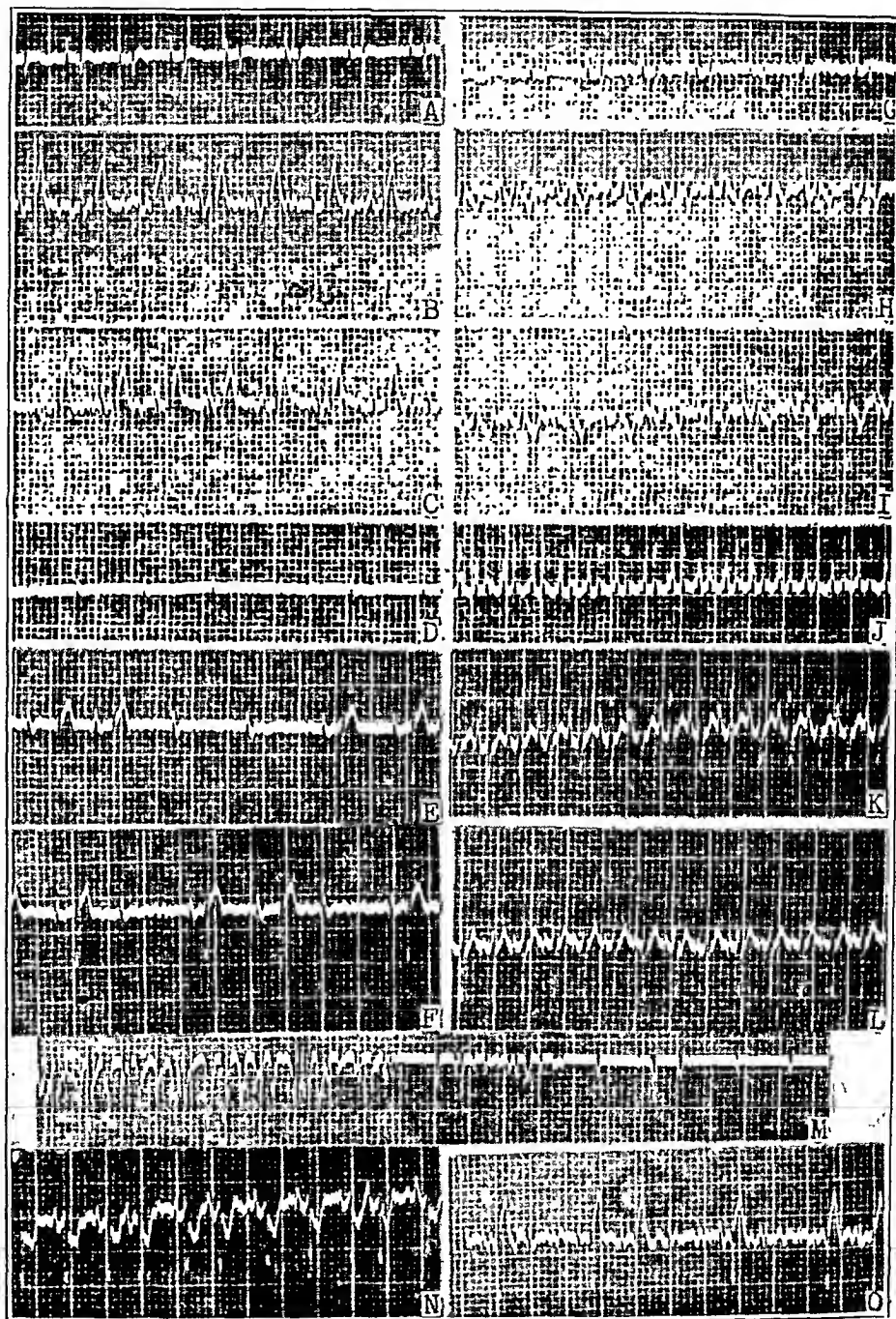


Figure 1

*(See legend on opposite page)*

most pigeons, and in several instances varying degrees of heart block resulted (figure 1 *D, E, F* and *O*). In spite of continued vomiting the cardiac rates of the 6 birds on the acute regimen increased several days later and reached a maximum, usually during opisthotonos, on about the fourteenth day. In the 2 birds with abnormal electrocardiograms, however, the rates were much faster than in the others (330 and 360, respectively).

With 2 exceptions, tachycardia, frequently marked (cardiac rates of 390, 480, 480 and 480 per minute, respectively), appeared in chronically deficient pigeons with abnormal electrocardiograms. The frequency of the heart beat increased gradually for several days before the electrical changes became manifest and perhaps became faster in animals with marked electrocardiographic changes, i.e., a cardiac rate of 480 per minute, than in those with mild changes, i.e., cardiac rates of 330 and 360 per minute.

When thiamine hydrochloride or thiamine pyrophosphate (20 to 50 micrograms) was administered intramuscularly the cardiac rate was noted to slow gradually during one to three days to, or nearly to, normal, although the electrocardiogram returned to normal in one or two hours.

Repair Experiments: Four pigeons with similar inversion of the T waves were given 10 micrograms of thiamine hydrochloride (2 instances) and 12.5 micrograms of cocarboxylase (2 instances) intravenously, and the electrical activity of their hearts was studied at intervals of fifteen, thirty, sixty, ninety and one hundred and twenty minutes after the injection. In figure 2 *B, C, D* and *E* are shown a series of such records (lead II) from a pigeon which received 12.5 micrograms of cocarboxylase (figure 2 *A* is a control normal electrocardiogram from this same bird). In one hour the inverted and

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#### EXPLANATION OF FIGURE 1

(The tips of the QRS complexes in leads II and III have been reenforced with white ink; otherwise they would not be reproduced.) *A, B* and *C*, the normal conventional leads I, II and III from pigeon 337 (rate 180 per minute). *D, E* and *F*, leads I, II and III, showing bradycardia (rate 120 per minute). Note the variable heart block and the normal configuration of the waves. *G, H* and *I*, leads I, II and III, illustrating the electrocardiographic abnormality observed most frequently in thiamine-deficient pigeons. Note the changes in the T waves in leads II and III and the short initial deflection upward of the QRS complex (rate 240 per minute). *J, K* and *L*, leads I, II and III, showing a type of electrocardiographic abnormality observed less frequently in thiamine-deficient pigeons. Note QRS complexes in leads I and II. *M*, lead I, recording ventricular fibrillation alternating with ventricular asystole in a thiamine-deficient pigeon just before death. *N*, lead II, showing marked inversion of the T wave (rate 300 per minute). *O*, lead II, showing variable heart block (rate 150 per minute).

depressed T waves had returned to normal. In another instance (fig. 1 *N*) a slightly more inverted and depressed T wave was restored to normal in ninety minutes by an identical injection. In 2 other instances similar restoration to normal followed the injection of 10 micrograms of

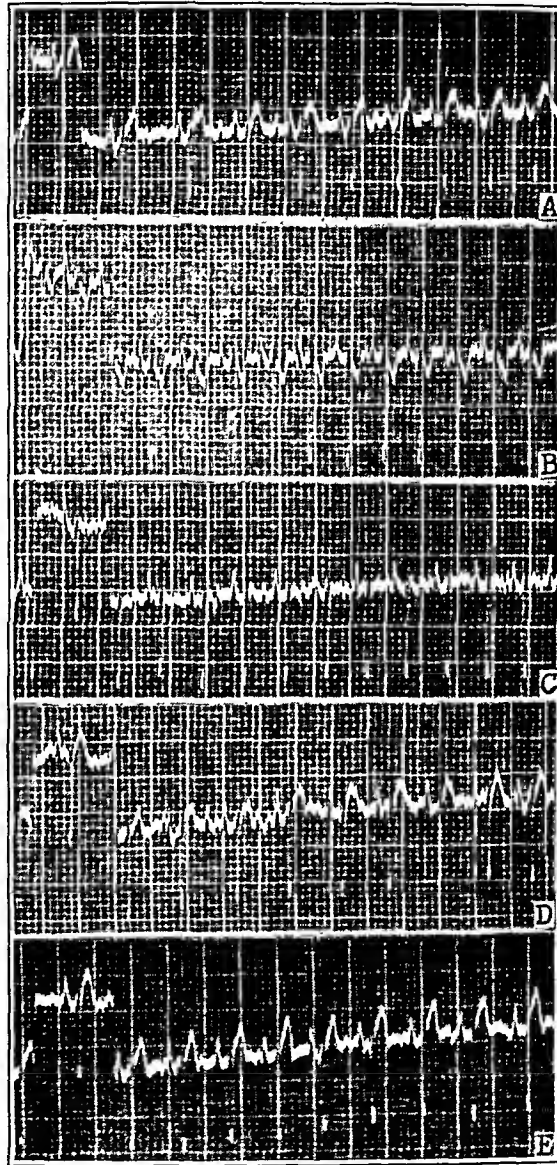


Fig. 2.—(The tips of the QRS complexes in leads II and III have been reinforced with white ink; otherwise they would not be reproduced.) The rapid response of electrocardiographic abnormality (lead II) to the administration of cocarboxylase (or thiamine pyrophosphate) intravenously. *A*, a record made one day before the cocarboxylase was given; it is essentially normal (rate 210 per minute). *B*, the T waves are depressed (rate 300 per minute). *C*, a record made fifteen minutes after 12.5 micrograms of cocarboxylase was given intravenously. Records were also made thirty (*D*) and sixty (*E*) minutes after the administration of cocarboxylase.



thiamine hydrochloride, and in a third the pigeon responded in like manner to 20 micrograms of thiamine hydrochloride.

On several occasions small increases in the thiamine hydrochloride intake (1 to 2 micrograms) restored moderately abnormal T waves to normal, or contrarily, an identical decrease in the thiamine increased the degree of abnormality. On these occasions the daily food intake was 20 Gm. and the thiamine hydrochloride intake approximately 16 micrograms. The sensitivity of the balance of available and of required thiamine and its effect on the metabolism of the heart muscle are evident from these observations.

**Pathologic Studies:** The hearts of 9 of these pigeons were studied histologically. Early changes consisting of loss of cross striations and development of wavy fibrous appearance and pale staining reactions of muscle fibers were encountered in all but one heart, and in several of them small areas of necrosis with polymorphonuclear cell infiltration were also seen. Hydropericardium or other gross evidences of cardiac failure were found in but 4 pigeons, all chronic. Both necrosis of the myocardium with polymorphonuclear cell infiltration and evidences of cardiac failure occurred less frequently in this group of birds than in previous groups of more chronic pigeons (see section headed Comment).

**The Concentration of Cocarboxylase:**<sup>13</sup> This factor, expressed as micrograms per gram of tissue, was determined in a number of normal and of thiamine-deficient pigeons. The hearts of normal pigeons contained 4.5 to 5.5 micrograms; in 2 pigeons on a thiamine-deficient diet but with no electrocardiographic changes there were 1.9 and 2.2 micrograms, respectively, and in 6 pigeons with abnormal electrocardiograms and no evidences of cardiac failure there was 1.5 to 1.7 micrograms of cocarboxylase per gram of heart muscle. The hearts from other more chronic pigeons with hydropericardium or other evidence of cardiac failure contained 1.2 to 1.4 micrograms of cocarboxylase per gram of tissue.

#### COMMENT

It seems clear that fulfilment of several experimental conditions leads<sup>1</sup> to the development of signs of cardiac failure in thiamine-deficient pigeons. The same is true of dogs.<sup>4</sup> First, the daily food intake should be sufficient to prevent a significant loss of weight. Twenty grams of diet accomplished this ideally, and in many instances produced a slight gain in weight. In practice, however, 15 Gm. proved adequate and was frequently more expedient, since there was less tendency for the smaller

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13. In another study being prepared for publication the amount of thiamine (as cocarboxylase) was determined in the heart, brain, liver, breast muscle and other tissues from pigeons both on the acute and on the chronic regimen. The figures used in the present paper were borrowed from that study.



amount to be vomited. A further reduction of the food intake tended to prevent the development of cardiac failure, probably because this lowered the metabolic rate.<sup>14</sup> Second, the thiamine intake should be adjusted so that the deficiency develops slowly. An intake of 60 to 80 per cent of the normal requirement (15 to 20 micrograms of thiamine hydrochloride for each 20 Gm. of diet<sup>15</sup>) has proved most efficient in this respect, as it prevents opisthotonos, yet allows thiamine depletion in the heart (and other tissues) to continue. The addition of this much thiamine to the diet also prevents vomiting. Finally, the situation created by these two conditions must exist long enough for the signs of cardiac failure, e. g., hydropericardium, to develop. This may take one to seven days. Our observations indicated also that activity favors the development of signs of cardiac failure. This was also noted in human beings by Keefer.<sup>16</sup>

Thiamine pyrophosphate (cocarboxylase), a coenzyme, is the form in which thiamine is used by the cell. This compound is an important link in the chemical mechanism by means of which heart muscle and other cells obtain their energy. In pigeons receiving 20 Gm. of diet daily and no thiamine (acute regimen), the depletion of cocarboxylase from the myocardium during the first week is rapid. Thereafter, however, depletion occurs more slowly. A comparison of the analytic data with the corresponding electrocardiograms indicates that abnormal electrical potentials are not produced by a pigeon's myocardium unless the cocarboxylase content falls below 2 micrograms per gram of heart tissue. This low figure is rarely reached in acutely deficient birds before opisthotonos develops and death ensues. However, if after the first week of experimentation the acute regimen is replaced by a chronic regimen (one partially free of thiamine), the length of the experiment can be extended. In this way a further reduction in the cocarboxylase content of the myocardium occurs, and its impairment, as indicated by changes in the electrocardiogram, results. This is followed by degeneration of myocardial fibers. If the metabolic rate is normal and impaired function is present long enough, signs of cardiac failure will develop. On the other hand, if animals have been starved, evidence of congestive cardiac failure will be absent, even though tachycardia is present, the electrocardiogram is abnormal and many myocardial fibers are degenerated. This seems to have occurred in the dogs of Porto and de Soldati.<sup>16</sup> An abnormal electrocardiogram and tachycardia seem

14. Unpublished studies revealed that the total oxygen consumption of fasting pigeons or pigeons consuming a thiamine-free ration ad libitum frequently falls as much as 30 to 50 per cent.

15. Twenty-five micrograms of thiamine hydrochloride is required for the normal metabolism of 20 Gm. of diet II.<sup>9</sup>

16. Porto, J., and de Soldati, L.: Alteraciones microscópicas del corazón del perro en avitaminosis B<sub>1</sub>, *Rev. Soc. argent. de biol.* **15**:303, 1939.

to indicate accurately that the cocarboxylase content of the myocardium is low but are no assurance that evidences of cardiac failure are present.

The abnormal electrocardiographic waves in our thiamine-deficient pigeons were similar to those observed in thiamine-deficient rats<sup>7c</sup> and dogs<sup>6</sup> and in human beings with infarcted myocardiums. In cases of thiamine deficiency these changes are probably due largely to functional impairment rather than histologic degeneration of muscle fibers, since they may be so quickly restored to normal by thiamine and so few fibers degenerate. Tachycardia developed in our tube-fed thiamine-deficient pigeons, whereas according to other authors, bradycardia<sup>5</sup> developed in pigeons fed various thiamine free diets ad libitum. The reason for this discrepancy appears to rest with the fact that our birds were well nourished and active, whereas those that feed voluntarily are almost always emaciated. This explanation is supported by the presence of marked bradycardia in our starved control pigeons, and the conclusion of other investigators<sup>8</sup> that bradycardia in thiamine-deficient rats may be due to concomitant starvation.

Weiss, Haynes and Zoll<sup>7c</sup> found that the heart rate of thiamine-deficient rats with bradycardia and abnormal electrocardiograms rapidly increased to normal when thiamine was given; the electrocardiograms also returned to normal. This occurred even though the rats fasted both before and during this curative response, so that the response seemed to be specific for thiamine. McEachern noted similar increases in the contraction rates of hearts from thiamine-deficient rats in vitro when thiamine was added to the solution containing the heart.<sup>17</sup> These and other evidences show that under certain circumstances thiamine deficiency does reduce the heart rate.

The appearance of tachycardia in our pigeons a day or so before the electrocardiograms had been altered, and at times even in the absence of such changes entirely, suggests the operation of additional factors. Possible mechanisms are suggested by the arteriolar dilatation noted in human veins by Weiss,<sup>18</sup> and by the hyperemia and hemorrhages which appear in the brains of severely thiamine-deficient pigeons.<sup>19</sup>

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17. These results were presented before the Neurological Society of Montreal, during the year 1940 to 1941.

18. Weiss, S.: Occidental Beriberi with Cardiovascular Manifestations, *J. A. M. A.* **115**:832 (Sept. 7) 1940.

19. Prickett, C. O.: The Effect of a Deficiency of Vitamin B upon the Central and Peripheral Nervous Systems of the Rat, *Am. J. Physiol.* **107**:459, 1934. Alexander, L.; Pijoan, M.; Myerson, A., and Keane, H. N.: Beriberi and Scurvy: An Experimental Study, *Tr. Am. Neurol. A.* **64**:135, 1938. Zimmerman, H. M.: The Pathology of the Nervous System in Vitamin Deficiencies, *Yale J. Biol. & Med.* **12**:21, 1939.

Recent studies of the mechanisms whereby these hemorrhages are produced<sup>20</sup> revealed that vascular dilatation preceded hemorrhage and was followed by a perivascular accumulation, first of fluid, then of red cells. Infiltrating hemorrhages developed later and in the more severely deficient pigeons only. In the acutely deficient pigeons with opisthotonos vascular dilatation and occasionally perivascular hemorrhages were seen only in the vestibular nucleus and other nuclei which were affected early by thiamine deficiency. The present study indicates that even such localized vascular changes were accompanied by a slight increase in the pulse rate, although no changes occurred in the electrocardiograms. In the more chronic animals, such as those in which marked tachycardia and marked electrocardiographic abnormalities developed, vasodilatation with few or no hemorrhages was to be found throughout the entire brain and in the liver, kidneys, lungs and other viscera. The effect of these multitudinous arteriovenous shunts on peripheral vascular resistance must have been great and is reflected in the tachycardia which was present in some of these birds.

The fact that in all instances vascular lesions were secondary to histologic changes in the neurons<sup>20</sup> leads to the belief that the tissue metabolic changes consequent to thiamine deficiency caused the dilatation of the blood vessels (and in certain cases led to extravasation from them of plasma and red cells).

It seems likely, therefore, that the manifestations of cardiac failure in thiamine deficiency are due to at least two factors. The first of these, vasodilatation, is due to the action of intermediate products of carbohydrate metabolism on the blood vessels. The extent of this change determines the peripheral vascular resistance and the speed of the heart rate. This may also account, in part if not entirely, for the hydropericardium, pulmonary edema and edema of the dependent parts of the body, since fluid readily extravasates through markedly dilated blood vessels. The second factor is the effect of thiamine deficiency on the myocardium directly. No doubt this has a tendency to impair the function of the heart and thus lower its reserve and eventually leads to cardiac standstill. The part that this factor plays in the production of edema is uncertain, although no doubt important. The two factors operating together produce a so-called "vicious cycle" and frequently result, rather suddenly, in what appears to be left ventricular failure,

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20. Swank, R. L., and Prados, M.: Avian Thiamine Deficiency: II. Pathologic Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relation to the Clinical Behavior, *Arch. Neurol. & Psychiat.* **47**:97 (Jan.) 1942. Prados, M., and Swank, R. L.: Vascular and Interstitial Cell Changes in Thiamine-Deficient animals, *ibid.* **47**:626 (April) 1942.

followed by death both in pigeons and in dogs<sup>4</sup> and possibly also in human beings.<sup>18</sup>

In contrast to well fed thiamine-deficient animals, those with a low caloric intake are less apt to accumulate intermediate products of carbohydrate metabolism in their tissues, since far less carbohydrate is metabolized. Hence, the first factor, vasodilatation, is nonoperative. In addition, the metabolic rate of the animal is reduced, and a less rapid blood flow suffices for its metabolic needs. The second factor, direct effect of thiamine lack on the myocardium, is operative and in the absence of any opposing mechanism results in a marked slowing of the heart. This dual mechanism appears to explain why bradycardia has been observed by some investigators and tachycardia by others in thiamine-deficient mammals. It is interesting that the thiamine-deficient dogs of Porto and de Soldati had tachycardia and abnormal electrocardiograms but no evidences of congestive cardiac failure. It is likely that vasodilatation was mild or moderate, rather than extreme, in these dogs, since starvation was so marked and fluid did not extravasate from the blood vessels. Recently de Soldati has summarized his work on, and his interpretations of, thiamine deficiency both in human beings and in animals.<sup>21</sup>

#### CONCLUSION

1. A chronic deficiency of thiamine without starvation will produce signs of cardiac failure in pigeons.

2. This is preceded and accompanied by tachycardia and electrocardiographic abnormalities.

3. Necrosis of myocardial fibers with inflammatory cell infiltration occurs frequently, although late, in thiamine-deficient pigeons.

4. The electrocardiographic abnormalities and evidences of cardiac failure in thiamine-deficient pigeons are accompanied by marked decrease in the cocarboxylase content of the heart muscle.

5. The electrocardiographic abnormalities and the evidence of cardiac failure, if not too severe, respond immediately to treatment either with thiamine hydrochloride or cocarboxylase.

6. Starvation alone or during thiamine deficiency produces bradycardia and frequently variable heart block in pigeons.

7. The methods and mechanism by which tachycardia and evidences of cardiac failure are produced in thiamine deficiency are presented and discussed. It is suggested that the tachycardia is due to vasodilatation, which is caused by the local accumulation of intermediate products

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21. de Soldati, L.: *Los trastornos circulatorios de la avitaminosis B<sub>1</sub>*, Buenos Aires, El Ateneo, 1940.

of carbohydrate metabolism. This also facilitates transudation of fluid from blood vessels to form hydropericardium and other evidences of cardiac failure. In addition, thiamine deficiency impairs the function of the heart, increases the tendency to extravascular fluid collections and results in terminal cardiac standstill. It seems probable that thiamine deficiency, in the absence of peripheral vasodilatation, causes bradycardia, but unfortunately most experiments involving such deficiency have been complicated by marked starvation, which also is known to cause bradycardia.

# SULFONAMIDE COMPOUNDS IN THERAPY OF BACTERIAL ENDOCARDITIS

A COMPARISON OF THE IN VITRO INHIBITORY EFFECTS AND THE  
BACTERIOSTATIC ACTIVITY

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AND

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DURHAM, N. C.

Since the introduction of sulfonamide compounds into clinical medicine new interest has been awakened in the chemotherapy of bacterial endocarditis. In recent years the clinical effectiveness of these compounds has been demonstrated<sup>1</sup> in a small yet hopeful number of patients suffering from this generally fatal disease. In a previous communication<sup>2</sup> considerable variability was noted in the inhibitory effects in vitro of sulfonamide compounds on the growth of certain organisms isolated from human beings with bacterial endocarditis. The preliminary subjecting of each organism to the reaction of the several drugs in vitro prior to the institution of therapy would seem to be a rational and important procedure, provided that in vitro inhibition can be correlated with clinical bacteriostatic activity. Opinion with regard to the degree of correlation of in vitro and in vivo (animal experiments) studies is divided.<sup>3</sup> Long and Bliss<sup>4</sup> expressed the belief

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1. Lichtman, S. S., and Bierman, W.: The Treatment of Subacute Bacterial Endocarditis: Present Status, *J. A. M. A.* **116**:286-289 (Jan. 25) 1941.

2. Poston, M. A., and Orgain, E. S.: A Comparison of the Effects of the Sulfonamide Drugs upon the Growth of Twenty-Five Organisms Isolated from Twenty-One Patients Suffering from Bacterial Endocarditis, to be published.

3. (a) Whitby, L.: Chemotherapy of Bacterial Infections, *Lancet* **2**:1095-1102, 1938. (b) Hoare, E. D.: Bactericidal Changes Induced in Human Blood and Serum by Sulphamido-Chrysoidine and Sulphanilamide, *ibid.* **1**:655-659, 1938. (c) MacLean, I. H.; Rogers, K. B., and Fleming, A.: M. & B. 693 and Pneumococci, *ibid.* **1**:562-568, 1939. (d) Schmidt, L. H.; Hilles, C.; Dettwiler, H. A., and Starks, E.: The Response of Different Types and Strains of Pneumococcus to Sulfapyridine, *J. Infect. Dis.* **67**:232-242, 1940. (e) Libby, R. L., and Joyner, A. L.: The Action of Sulfathiazole on the Colon-Typhoid-Dysenteriae Group of Organisms, *ibid.* **67**:67-69, 1940.

4. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939, pp. 96 and 110.

that there is an appreciable degree of correlation but that parallelism ceases when relative susceptibilities of different organisms in cultures and their reactions in the animal body are compared. The only available study on bacterial endocarditis in human beings is that of Swain,<sup>5</sup> who demonstrated a definite correlation in 4 cases of endocarditis caused by *Streptococcus viridans*. It is the purpose of this paper to show the existence of a broad correlation between in vitro inhibition and clinical bacteriostatic activity and to emphasize the importance of preliminary in vitro experiments before drug therapy is begun.

#### MATERIAL AND METHOD

During the past three years 17 patients admitted to Duke Hospital with classic bacterial endocarditis have been given chemotherapy. The agents employed included one or more of the following seven compounds: sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sodium sulfapyridine, N<sup>4</sup>-sulfanilylsulfanilamide, sodium N<sup>4</sup>-sulfanilylsulfanilamide, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-methylthiazole). From the blood of these patients the following organisms have been isolated: eleven strains of *Str. viridans*, two strains of *Streptococcus haemolyticus*, one strain of anaerobic *Streptococcus* (nonhemolytic), three strains of *Streptococcus faecalis*, one strain of *Neisseria gonorrhoeae*, one strain of *Haemophilus parainfluenzae* (hemolytic) and one strain of *Brucella suis*. In 3 instances two species of organisms were isolated from a single patient. Prior to the institution of chemotherapy, we determined the inhibitory effects of sulfanilamide and those of its derivatives then available on the growth of the organism isolated from the patient.<sup>6</sup> Generally, the drug showing the greatest bacteriostatic effect was used for treatment, and for 6 patients two or more drugs were tried in rotation for periods of not less than one week each.

Three to seven blood cultures positive for the causative organism were obtained on each patient prior to therapy, and two to three blood cultures<sup>7</sup> were made weekly throughout the remainder of their stay in the hospital.

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5. Swain, R. H. A.: Strain Variations in the Resistance of *Streptococcus Viridans* to Sulphonamide Compounds, *Brit. M. J.* **1**:722-725, 1940.

6. The technic of these in vitro experiments has been reported in a previous paper, in which the inhibitory effects of six of the drugs most frequently used clinically were tested. For compounds administered orally in vitro inhibition was determined for twenty-four hour intervals, while for those given intravenously intervals of one, two, three, four and twenty-four hours were employed.

7. Since the suggestion of Strauss, Lowell and Finland (*J. Clin. Investigation* **20**:189, 1941) with regard to the addition of paraaminobenzoic acid to a laboratory medium, we have used it in 4 cases in addition to our previous paraaminobenzoic acid-free medium as a control to test the validity of blood cultures negative for the organism under consideration. The results were identical in both mediums; i. e., in 3 patients blood cultures made on both mediums during therapy became negative simultaneously, and in 1 patient cultures on both mediums remained equally positive. When explants of blood containing a sulfonamide compound are made, the concentration of that compound is reduced considerably by dilution in routine blood cultures.

TABLE 1.—Comparison of the *In Vitro* Effects and the Clinical Bacteriostatic Activity of Sulfanilamide and Six Derivatives Administered Orally

Patient Number	Organism	Drug	In Vitro Experiment: Lowest Level of Drug and Time Necessary for Complete Inhibition of Growth		Average Daily Blood Drug During Oral Admin- istration, Mg./100 Cc.	Total Number of Blood Cultures	Average Number of Colonies per Cc. of Blood			Correlation Group
			Drug, Mg./100 Cc.	Time, Hours			Before Therapy	During Therapy	After Therapy	
1	<i>N. gonorrhoeae</i> Anaerobic streptococcus	Sulfapyridine	3.9 3.9	24 24	4.4	15	<1 <1	0 0	0 0	I I
2	<i>S. faecalis</i>	Sulfapyridine	4.0	24	4.0	9	3	0	Died	I
3	<i>S. viridans</i>	N <sup>4</sup> -Sulfanilyl- sulfanilamide Sodium N <sup>4</sup> -Sulfanilyl- sulfanilamide	2.0 Incomplete-10	24 24	2.7 2.0	63	2 1	0 114	1 100	I II
4	<i>S. viridans</i>	Sulfanilamide	10.4	24	10.7	6	502	1	Died	I
5	<i>H. parainfluenzae</i>	Sodium N <sup>4</sup> -Sulfanilyl- sulfanilamide	10	24	2.7	9	<1	<1	Died	II
6	<i>S. viridans</i>	N <sup>4</sup> -Sulfanilyl- sulfanilamide Sulfanilamide N <sup>4</sup> -Sulfanilyl- sulfanilamide Sulfanilamide	Incomplete-10 Incomplete-30 Incomplete-10 Incomplete-30	24 24 24 24	0.6 6.8 1.3 10.5	35	23 40 5 22	29 10 26 1	40 5 22 45	II II II III
7	<i>S. faecalis</i>	Sulfapyridine Sulfapyridine Sodium sulfapyridine Sulfapyridine Sulfapyridine Sodium sulfapyridine	7.5 Incomplete-10 Incomplete-30 Incomplete-10 Incomplete-30	24 24 24 24 24 24	3.0 2.9 5.2 3.0 2.9 5.2	31	8 9 26 15 20 5	5 22 13 0 11 4	9 26 17 20 5 6	II II II I II II
8	<i>S. faecalis</i>	Sulfamethylthiazole	Incomplete-10	24	7.2	6	38	18	51	II
9	<i>S. viridans</i>	Sulfamethylthiazole	Incomplete-10	24	5.8	5	17	6	14	II
10	<i>S. viridans</i>	N <sup>4</sup> -Sulfanilyl- sulfanilamide Sulfamethylthiazole Sulfathiazole	7.5 5.0	24 24	0.9 2.5 3.3	31	6 14 39	0* 0 9	14 39 14	III III II

\* Blood stream temporarily sterilized.



TABLE 2.—Comparison of the *In Vitro* Inhibitory Effects and the Clinical Bacteriostatic Activity of Sulfapyridine and Sodium Sulfapyridine Administered Intravenously and Orally

In Vitro Experiment:														
Patient Number	Organism	Drug	Lowest Level of Drug and Time Necessary for Complete Inhibition of Growth			Blood Level of Drug After Intravenous Injection, Mg./100 Cc.			Average Daily Blood Level of Drug During Oral Therapy, Mg./100 Cc.	Total Number of Blood Cultures	Average No. of Colonies per Cc. of Blood			Correlation Group
			Drug, Mg./100 Cc.	Time, Hours	Immedi-ately *	4 Hr.*	24 Hr.*	Before Ther-apy			Dur-ing Ther-apy	After Ther-apy		
11	S. viridans	Sodium sulfapyridine	20	3	.....	5.5	.....	3.7	38	14	0	0	I	
					43.5	8.2	.....	9.6 (17 hr.)						
12	S. viridans	Sodium sulfapyridine	15	3	16.4	37	.....	.....	27	17	0	6	I	
					18.0	.....	.....	.....	....	12	0	<1	I	
13	S. haemolyticus		5	3	19.8	.....	.....	.....						
	S. viridans	Sodium sulfapyridine	10	24	24.0	16.0	.....	11.0	22	85	0	0	I	
					.....	.....	.....	14.9 †						
					.....	.....	.....	13.3 †						
					.....	.....	.....	16.3 †						
14	S. viridans	Sodium sulfapyridine	15	24	.....	.....	.....	17.2 †	14	8	0	0	I	
					.....	.....	.....	23.3 †						
10	S. viridans	Sodium sulfapyridine	13.5	24	30.0	2.8	0.9 (16 hr.)	10.4	52	1	<1	6	II	
					9.0	.....	.....	.....						
9	S. viridans	Sodium sulfapyridine	15	24	7.8	3.5	.....	.....	14	25	6	17	II	
					27.0	11.4	.....	.....						
					24.0	14.0	3.1	.....						
					20.2	13.2	.....	.....						
8	S. faecalis	Sodium sulfapyridine	Incomplete-30	24	21.3	.....	.....	7.5 (18 hr.)	20	4	3	38	II	
					.....	.....	.....	20.1 †						
15	S. viridans	Sodium sulfapyridine	Incomplete-60	24	11.8	6.0	.....	.....	13	80	201	143	II	
					20.5	11.0	9.5	.....						
					35.2	14.7	.....	.....						
16	Dr. suls	Sodium sulfapyridine	20	24	9.0	4.8	.....	10.9	58	9	0	11	III	
					17.0	13.9	8.6	.....						
					30.0	25.0	10.8	.....						
17	S. viridans	Sulfapyridine (in 25% dextrose)	25	24	.....	13.2	.....	.....	7	98	0	Died	III	
					.....	11.0	.....	6.1 (12 hr.)						
					.....	24.4	.....	7.8 (9 hr.)						
					.....	21.8	.....	19.0 (10 hr.)						

\* Blood level after a single daily intravenous injection of the drug.

† Average blood level during forty-eight hours of continuous intravenous drip therapy.

‡ Average of four to eight determinations of blood level during intravenous injection of single doses at four hour intervals.

Sodium sulfapyridine was administered intravenously at first and later orally to 9 patients. Sulfapyridine in 25 per cent dextrose solution was given to 1 patient. All other drugs were administered orally in the maximum tolerated dose in the majority of instances. Intravenous administration was carried out in three ways, namely, continuous intravenous drip (1 patient), large single daily doses (8 patients) and smaller doses given regularly at four hour intervals for forty-eight to seventy-two hours (2 patients). After large single doses of sodium sulfapyridine the concentration of the compound in the blood was determined immediately at the end of the injection, four hours later and at various intervals thereafter up to twenty-four hours in most instances. During continuous drip therapy or after repeated four hour doses of the drug, its concentration in the blood was determined fairly regularly at four hour intervals. During oral chemotherapy blood levels were determined daily in many instances and at least two to three times weekly in the remainder. The figures in tables 1 and 2 represent average daily colony counts of blood cultures and blood levels of the drug administered.

TABLE 3.—*Summary of Results of Experiments on In Vitro Inhibition and In Vivo Bacteriostatic Activity of Sulfanilamide and Six Derivatives Administered Orally and Intravenously*

Group		Method of Administration of Drug	
		Oral	Intravenous
I	In vivo concentration of drug equal to in vitro inhibitory level—Bacteriostasis present .....	6	5
II	In vivo concentration of drug below in vitro inhibitory level—Bacteriostasis absent .....	13	4
III	In vivo concentration of drug below in vitro inhibitory level—Bacteriostasis present .....	3	2
	Total .....	22	11

In the entire group of 17 patients, from whom 20 organisms were obtained, a sulfonamide compound was administered a total of twenty-eight times, giving 33 clinical experiments for purposes of correlation.

#### RESULTS AND COMMENT

The data showing the correlation of in vitro and in vivo inhibitory action in each of the 33 clinical experiments are presented in tables 1 and 2. The division of patients on the basis of oral or intravenous administration of the drugs is arbitrarily used for purposes of comparing the two methods. The figures for in vitro inhibition represent concentrations at which complete inhibition of growth of the organisms was produced; partial inhibition was disregarded for purposes of correlation. In vivo inhibition was considered only when there was significant bacteriostasis, i. e., marked diminution of the colony counts of blood cultures, or when sterilization of the blood was effected.

The correlation experiments are divided into three groups for purposes of clarity, and the results are summarized in table 3. In group I are recorded those instances in which marked inhibition of the growth of organisms or actual sterilization of the blood stream was produced

when the blood concentration of the drug equaled or surpassed the in vitro inhibitory level. Group II comprises those experiments in which significant bacteriostasis was absent when the blood concentration failed to reach the in vitro level. Group III is composed of those instances in which marked inhibition of the activity of organisms in the blood stream was effected by a lower blood concentration of the drug than the in vitro inhibitory level. When the in vivo level reached and maintained the in vitro level, no discordant failures were encountered.

In the group of patients given the drugs orally the effects of seven compounds on twelve strains of organisms from 10 patients have been observed in 22 clinical experiments. In 19 instances (groups I and II) the clinical result was in accord with the result of the in vitro experiment. In 5 of these when the blood concentration reached or surpassed the in vitro inhibitory level sterilization resulted, and in 1 instance there was marked inhibition (group I). It is to be noted that some of the strains (in patients 1, 2, 3 and 7) were sensitive at low in vitro inhibitory levels, which were within the range easily obtainable by oral administration of the drugs. In the remaining 13 experiments (group II) the blood concentration of the drugs never attained the in vitro levels, and neither significant inhibition nor sterilization was obtained. Here, the in vitro inhibitory levels were generally high and above easily attained clinical levels, indicating resistance of the organisms to the action of drugs used in chemotherapy (patients 3, 5, 6, 8 and 9). Group III comprises 3 instances in which the concentration of the drug in the blood failed to reach the test tube inhibitory level. In 2 of these marked inhibition was effected, and in 1 sterilization resulted. In spite of relatively high in vitro levels (patients 6 and 10) bacteriostasis was obtained at lower in vivo levels. These apparently discordant results may indicate that the in vitro levels were unnecessarily high and are explainable on the basis of the heavy inoculum used in in vitro experiments in contrast to the small number of organisms circulating in the blood stream.

The group of patients given the drugs intravenously comprises 11 clinical studies of the effects of two drugs on eleven organisms in 10 patients. In 9 instances the in vivo result was consonant with the in vitro experiment. In 5 instances (group I) sterilization resulted when the in vitro level was reached in the blood stream. In 3 instances (patients 11 and 12 [2 strains]) the time required for test tube inhibition was short (three hours) at levels attainable (20, 15 and 5 mg. per hundred cubic centimeters), while in the other 2 (patients 13 and 14) the time interval was long (twenty-four hours), but the concentration (10 and 15 mg. per hundred cubic centimeters) was maintained intravenously, and sterilization was accomplished. In the 4 instances comprising group II (patients 10, 8, 9 and 15) neither inhibition nor sterilization was obtained when the in vitro level was either not reached or not maintained for the

required interval of time. The concentrations required here were relatively high (60, 30, 15 and 13.5 mg. per hundred cubic centimeters) and the intervals long (twenty-four hours). Sterilization resulted in both instances (patients 16 and 17) in group III, when the required blood concentration was reached but not maintained for the time interval necessary for inhibition.

From an analysis of the data of these experiments we conclude that a suggestive correlation exists between the results of the *in vitro* inhibitory experiments and the *in vivo* bacteriostatic action of the compounds used. That the correlation should be inexact is to be expected, because of the great differences between the conditions existing in the test tube and those factors in the heart valve and in the blood stream responsible for the growth of organisms in patients with bacterial endocarditis. In test tube experiments a relatively heavy inoculum was used, while in cases of bacterial endocarditis there is a growing focus of infection within the heart valve, which sheds fairly constantly a small number of bacteria into the circulating blood. It should be noted that in most instances when the *in vitro* inhibitory level was low or the time required for inhibition was short, the concentration of the drug in the blood reached and maintained this level. In the majority of instances, however, the test tube level was higher than that which could be attained easily in the patient's blood. It is to be remembered that the test tube levels reported here represent only complete inhibition of the growth of organisms produced by the drug acting in a definite interval of time. These levels, since partial *in vitro* inhibition was disregarded, may well be too high and unnecessary in the blood, or the length of time required for drug action may be too long.

It seems from the discordant results that although sterilization or inhibition of growth may result in a lower concentration of the drug in the body than in the test tube, the converse is not true. The fact that no failures of sterilization resulted when the *in vitro* level of a drug was equaled by its *in vivo* level for the required length of time suggests that preliminary *in vitro* testing of compounds may indicate a helpful therapeutic blood level to be obtained in the patient during therapy. The data are insufficient but suggest that the most effective drug can be selected by *in vitro* experiments. This extremely important and practical point is difficult to settle by experimentation on human subjects, since the drugs must be given in simple rotation and "resistance, or fastness," of the organism frequently develops to several drugs of the sulfanilamide series after one of them has been therapeutically administered.<sup>8</sup> Animal experimentation may yield misleading results unless

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8. Poston, M. A., and Orgain, E. S.: Unpublished data. Lowell, F. C.; Strauss, E., and Finland, M.: Observations on the Susceptibility of *Pneumococci* to Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole, *Ann. Int. Med.* **14**:1001-1023, 1940.

concentration of the drug in the blood is known and controlled and is frequently impossible, since many organisms pathogenic for human beings are relatively nonpathogenic for animals.

Factors to be considered in comparing results of *in vitro* and of *in vivo* studies are the use of freshly isolated strains of organisms rather than artificially cultured laboratory strains; the size of inoculum for *in vitro* experiments; suitable nutrient medium free of neopeptone (Difco); careful checking of the concentrations of drug in the medium used; standard temperature of incubation; degree of inhibition, whether partial or complete; the pharmacologic properties of the drug used (solubility, absorption, excretion, acetylation), and the concentration of the drug in the animal body. It appears likely, as mentioned by Libby and Joyner,<sup>3e</sup> that when all factors are considered, the *in vitro* and the *in vivo* effects of sulfonamide compounds can be definitely correlated.

#### SUMMARY

The *in vitro* inhibitory effects of seven sulfonamide compounds on twenty organisms isolated from 17 patients suffering from bacterial endocarditis have been correlated with the clinical bacteriostatic activity of these drugs in a series of 33 clinical (*in vivo*) experiments.

A certain degree of correlation was found to exist between the *in vitro* inhibitory effects of these drugs and their clinical bacteriostatic activity.

The importance of preliminary *in vitro* experiments to determine the most effective drug and its possible clinical level of inhibitory action is emphasized.

Dr. David T. Smith contributed suggestions during the preparation of this paper. The sulfonamide compounds were supplied for experimental purposes by the Calco Division, American Cyanamid Company, Bound Brook, N. J.; the Winthrop Chemical Company, New York, and the Alba Pharmaceutical Company, New York.

Duke Hospital.

## ANTHRAX

### A REVIEW OF SIXTY CASES, WITH A REPORT ON THE THERAPEUTIC USE OF SULFONAMIDE COMPOUNDS

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CHESTER, PA.

Since March 1933 I have had the opportunity of making a diagnosis and instituting treatment in 60 cases of external anthrax. In 51 cases the patients were employees of a local mill engaged in the manufacture of inner lining. Its basic raw material is goat hair imported from China and India under existing regulations. In 4 cases the patients were children. Three of them (cases 3, 6 and 59) lived in the village in close proximity to the mill. They probably contracted anthrax while playing on ground contaminated with particles of hair, although their parents' hands or clothes (the parents worked in the mill) may possibly have been the source of infection. The fourth child (case 28), a girl of 12, contracted the disease after washing her father's work shirt. In case 40 the patient lived in the village and was the wife of a carder. She did not wash her husband's work clothes which were never brought to the house; hence the anthrax on her face was most probably due to contact with her husband's hands. A less likely source of infection in this case was possibly contaminated house dust. In another case (27) the patient was a Negro truck driver for a shipping concern that hauled and stored bales of hair for the local mill. Since this man had not come in direct contact with hair for over two months, the "pustule" on his neck must have been the result of infection contracted from contamination of his hands or clothes with hair dust left on the truck, in the warehouse or on the broom which the patient used for sweeping. In the 3 remaining cases (4, 34 and 41) the patients were employees of a Philadelphia plant that obtained its hair bobbins from the local mill. Two of them were weavers, while the third was a shipping clerk. A fourth case of anthrax also occurred in this plant, but the patient did not come under my care.

Forty-one patients were males, and 19 were females. Their ages ranged from 3½ to 62 years, but most of them were between 18 and 27. All but 1 were white. The yearly distribution of cases is shown in table 1. Forty-five per cent of them occurred in 1940 and 1941, indicating a sharp increase over the preceding years. This has undoubtedly

been due to the war and the resulting relaxation in the enforcement of control measures at the port of exit, as predicted by Smyth.<sup>1</sup> My cases occurred a few at the time, in rapid succession, indicating that the disease was caused by different shipments of hair, some of which were contaminated with spores of anthrax bacilli. Actually bacilli were recovered repeatedly from the center of various bales of hair, as well as from the dust left over in the combing process. This also explains the high inci-

TABLE 1.—*Yearly Distribution of Cases of Anthrax*

Year	Number of Cases	Number of Deaths
1933 .....	6	1
1934 .....	2	0
1935 .....	3	0
1936 .....	2	0
1937 .....	4	0
1938 .....	2	0
1939 .....	6	0
1940 .....	12	0
1941 .....	15	0
1942* .....	8	0
Total.....	60	1
Percentage.....		1.66

\* First six months of the year.

TABLE 2.—*Incidence of Anthrax in the Various Departments of the Local Mill*

Department	Number of Cases
Warehouse.....	4
Combing.....	23
Drawing.....	5
Spinning.....	16
Mending.....	2
Finishing.....	1
Total.....	51

dence of infection among the workers in the combing department, to which the disease was practically confined from 1933 to 1936. Thereafter, it appeared throughout the mill. The distribution of anthrax through the various departments is shown in table 2.

A definite history of trauma to the skin was elicited in many cases, but in a few the injury, if present at all, was so slight as to escape attention. It was also noted that while many an insignificant scratch

1. Smyth, H. F.: A Twenty Year Survey of Anthrax in the United States, Symposium on Anthrax, Commonwealth of Pennsylvania, Department of Health, April 1, 1941.

sustained on carding machines was followed by anthrax, several workers who suffered severe multiple lacerations and puncture wounds on the same machines did not contract the disease. This happy escape may be attributed to the vagaries of chance rather than to variations in individual susceptibility to anthrax.

Prompt medical attention to the wound (application of alcohol and tincture of iodine) did not prevent anthrax, and cauterization with phenol, which may have prolonged the incubation period in 2 cases, was soon discontinued because of the hazards involved in the careless application of this agent. The incubation period varied from twelve hours to five days. In most patients two to three days elapsed before the appearance of a papule. The diagnosis was made clinically and was confirmed in all cases but the last by smear and culture of material from the lesion made by Dr. George Sickel, of the Chester Hospital.

Virulence tests on some of the cultures isolated in these cases were performed at the Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pa., as follows: A culture of anthrax bacilli was isolated on May 17, 1936 (case 13, anthrax of elbow) before the administration of 200 cc. of antianthrax serum. A subculture grown on an agar slant was washed off with physiologic solution of sodium chloride, and by plate counts the stock solution was shown to contain 4,672,000 organisms per cubic centimeter. Virulence tests were made with a 0.5 cc. dose, administered subcutaneously as follows:

Guinea Pig No.	Material	Days of Observation*				
		1	2	3	4	5
1	Stock solution .....	L	L	D		+
2	Stock solution .....	L	L	D		+
1	1:10 dilution .....	L	L	L	D	+
2	1:10 dilution .....	L	L	L	D	+
1	1:100 dilution .....	L	L	L	D	+
2	1:100 dilution .....	L	L	L	D	+
Rabbit No.						
1	Stock solution .....	L	L	D		+
2	Stock solution .....	L	L	L	D	+
1	1:10 dilution .....	L	D			+
2	1:10 dilution .....	L	L	D		+
1	1:100 dilution .....	L	L	D		+
2	1:100 dilution .....	L	L	L	L	D
Sheep No.						
1	1:100 dilution .....	L	L	L	D	+
2	1:100 dilution .....	L	L	L	D	+
3	1:100 dilution .....	L	L	L	L	D

\* *L* signifies living and well; *D*, dead, and +, positive for anthrax bacilli.



On May 21 a second culture was isolated after 400 cc. of antianthrax serum had been administered. At that time, the temperature was normal, the edema was gone and the lesion was dry and black. This second culture killed guinea pigs, rabbits and sheep in the same degree as the first culture obtained before the administration of serum. A third culture made on May 25 was negative for anthrax bacilli.

Virulence tests were also made on two cultures isolated in case 23 (anthrax of the neck), in which the patient failed to respond to intensive sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy, and in case 24 (anthrax of the face), in which the patient was cured by sulfapyridine. The two cultures were suspended to 1,000,000,000 organisms per cubic centimeter in physiologic solution of sodium chloride (stock solution). Tests were made with a 1 cc. dose, administered subcutaneously as follows:

Guinea Pig No.	Material	Days of Observation*						
		1	2	3	4	5	6	7
Case 23								
1	Stock solution .....	L	D					+
2	Stock solution .....	L	L	D				+
1	1:100 dilution .....	L	L	D				+
2	1:100 dilution .....	L	L	L	D			+
1	1:1,000 dilution .....	L	L	D				+
2	1:1,000 dilution .....	L	L	L	L	L	L	
1	1:10,000 dilution . . . . .	L	D					—
2	1:10,000 dilution .....	L	L	L	L	L	L	
Case 24								
1	Stock solution .....	L	D					+
2	Stock solution .....	L	D					+
1	1:100 dilution .....	L	D					+
2	1:100 dilution .....	L	L	D				+
1	1:1,000 dilution .....	L	D					+
2	1:1,000 dilution .....	L	L	L	D			+
1	1:10,000 dilution .....	L	L	L	D			+
2	1:10,000 dilution .....	L	L	L	L	L	L	

\*L signifies living and well; D, dead; +, positive for anthrax bacilli, and —, negative for anthrax bacilli.

It is interesting to note that the culture obtained in case 24 was, if anything, a little more virulent than that obtained in case 23. Yet in the former case the patient was cured by sulfapyridine, even though treatment was started later than in case 23, in which the patient failed to respond to this drug. These tests show that highly virulent strains of anthrax bacilli were being dealt with.

The distribution of the lesions is shown in table 3. Twenty-five of them occurred on the face and neck—sites usually associated with the highest mortality rate.

The appearance of the lesions varied, depending on the time they were first seen (figs. 1 through 8). Early the lesion looked like a flea bite or an ordinary pimple. In a few hours it enlarged, looked fleshy and was yellowish. Soon its top turned brown, and often it was surrounded by a narrow ring of erythema. On the second day a few fine glistening vesicles usually developed at the periphery of the papule. As the vesicles enlarged, the depressed center of the papule ulcerated and turned dark brown, which color it remained until the third or fourth day, when it became black. The marginal vesicles, at first small and filled with a clear yellow gelatinous fluid rich in anthrax bacilli but poor in cellular content, enlarged in a day or two and then became bluish red

TABLE 3.—*Location of Anthrax "Pustule"*

Site	Number of Cases
Face.....	14
Neck.....	11
Arm.....	5
Forearm.....	10
Hand.....	5
Finger.....	13
Leg.....	1
Heel.....	1
Total.....	60

and discharged a serosanguineous fluid freely. On the fifth to the sixth day the central ulcer was covered by a tough black eschar, which gradually extended into the crusting peripheral vesicles. In many cases a wide area of erythema appeared around the papule on the second or the third day. Edema of the nonpitting variety developed early, twelve to twenty-four hours after the appearance of the papule, and soon spread well beyond its immediate vicinity. Thus, in case 23 (a "pustule" of the neck) the edema spread in ninety-six hours down to the level of the crest of the ilium. Similarly, in case 15 (anthrax of the forearm) the edema extended in seventy-two hours over the entire extremity and the upper portion of the chest. In cases 22, 23, 37, 46, 53, 54, 55 and 60 the anthrax edema was accompanied by or was actually preceded by tongue-like extensions of bright erythema of the skin. Under treatment the spread of the edema was checked first, and this was followed by its gradual disappearance (one to five days); then the papule became flat and dry, and finally the eschar separated at the edges and sloughed out

within seven to fourteen days, leaving a punched-out ulcer that usually healed in one to two weeks. The "pustule" was characteristically painless, but in a few cases there were pain and tenderness along the area of erythema. Local itching was an early and rather persistent complaint.



Fig. 1 (case 32).—The lesion is two days old and looks like a flea bite. The top of the papule is eroded and brown. A small amount of edema is present. Treatment was with sulfapyridine and sulfathiazole.

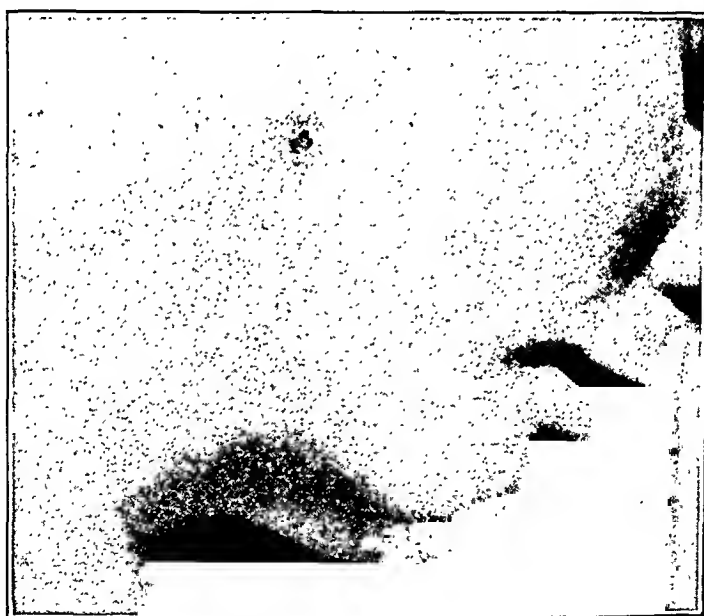


Fig. 2 (case 29).—The lesion shows characteristic central ulceration and a ring of vesicles. Notice that the angle of the jaw is obliterated by edema of the soft tissues overlying an enlarged lymph node. Treatment was with sulfapyridine.

Regional adenopathy, sometimes heralded by pain, developed in the great majority of the cases one to three days after the papule had appeared. The nodes varied in size from that of a pea to that of a

large walnut and were invariably painful and tender. The pain subsided promptly under treatment, but the lymphoid enlargement, though decreasing in size slowly, persisted throughout the duration of the papule and often lasted from a few days to two to six weeks after the ulcer had healed (cases 4, 21, 24, 31, 32, 40 and 57). Localized edema of the soft tissues overlying the enlarged lymph nodes was a common occurrence, and in cases 46, 53, 54 and 60 (anthrax of the hand, wrist, finger and forearm, respectively) there was bright erythema of the skin, in addition to swelling over the epitrochlear nodes. In cases 33 and 46 the appearance of adenopathy was associated with a sharp rise in tem-

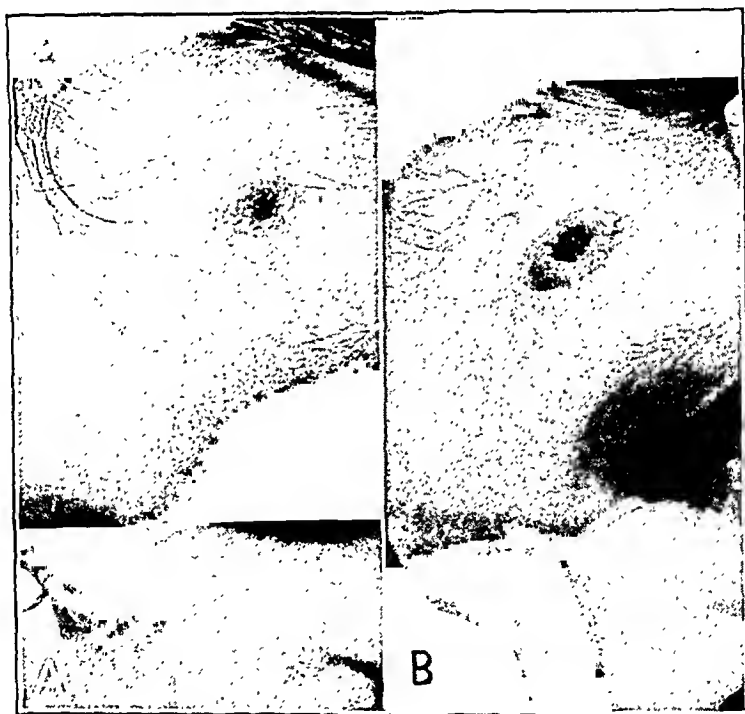


Fig. 3 (case 26).—*A*, the lesion shows a dry black eschar covering the central ulcer. Edema of the soft tissues is present. Treatment was with sulfapyridine and serum. *B*, the appearance of the lesion two days later. Notice the tenseness of the vesicles which form a ring around the central eschar. Extension of the edema has occurred, with involvement of the infraorbital space.

perature to 101 to 102 F., which subsided in twenty-four to forty-eight hours after therapy was intensified.

In some cases the patients also complained of headache and malaise. Before treatment was given, the temperature was normal in 11 cases, 99 to 100 F. in 36 cases and 100.6 to 102 F. in the remaining 13 cases. After treatment the temperature subsided in twenty-four to seventy-two hours.

Blood counts were done in 31 cases soon after the diagnosis of anthrax was made, and in all of them the red cell count and the hemo-

globin content were normal. The white cell count was below 8,500 in 15 cases, below 9,500 in 5 cases and between 10,500 and 13,500 in 11 cases. When present leukocytosis was of the neutrophilic variety. Blood cultures were negative for anthrax bacilli. Even in case 1 the blood culture made thirty-nine hours before death was negative for *Bacillus anthracis*, but at autopsy the organism was recovered from the heart, spleen, kidneys, etc. This is in agreement with Besredka's fundamental work, which proved that although an animal presents the typical picture of anthrax septicemia, the prime cause of death is cuti-infection

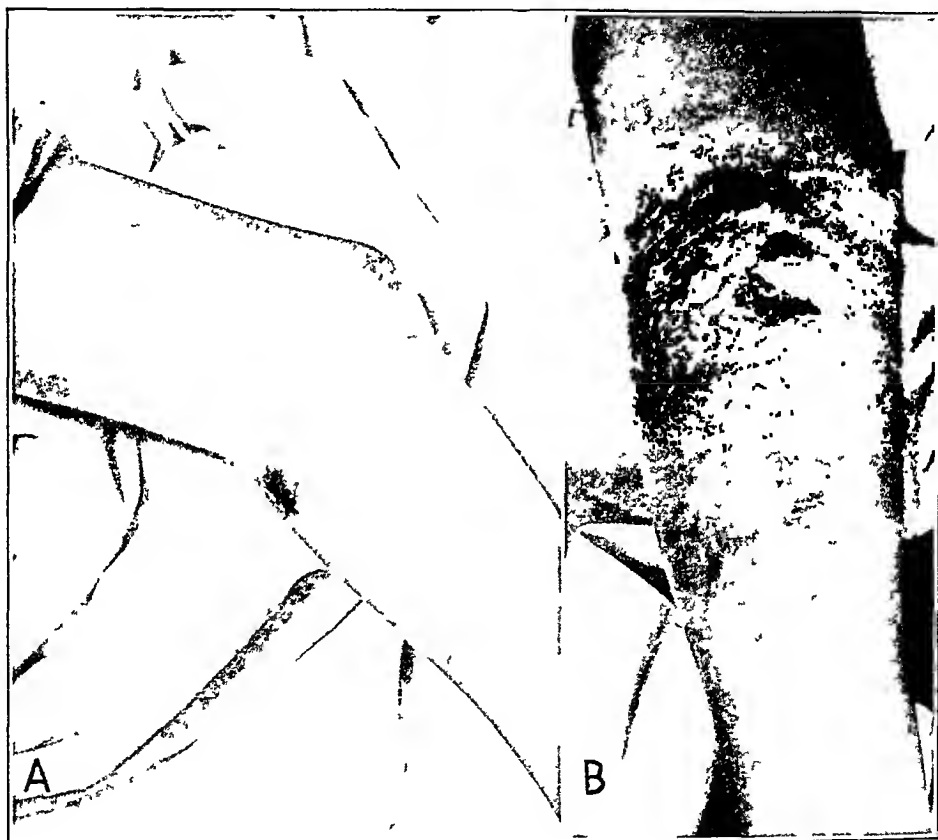


Fig 4 (case 15).—*A*, appearance of the lesion on the day of admission to Chester Hospital. The lesion is three days old. Note the raised blisters and the extensive edema of the upper third of the forearm and the elbow. *B*, the appearance of the lesion four days later. The skin around the "pustule" has become ecchymotic and covered with many large blisters. The entire extremity is markedly swollen from the fingers to the upper portion of the chest below the clavicle. The skin has split at the elbow. There was no pain, but the arm felt heavy. Treatment was with serum, neoarsphenamine and immunotransfusions.

and cuti-intoxication, since it is in the few minutes which precede the death agony phase that the eruption of the bacteria into the circulating blood takes place. Anthrax bacilli were recovered regularly during the various stages of the "pustule" and frequently after successful treat-

ment with antianthrax serum or with sulfapyridine. Thus, anthrax bacilli were recovered from the lesions in cases 2, 4, 8, 9 and 55 twelve, seven, seven, six and thirty-one days, respectively, after the administration of 740 cc., 1,200 cc., 1,200 cc., 1,000 cc. and 1,200 cc. of serum, respectively, and in cases 22 and 35 on the fourth and the seventh day, respectively, of sulfapyridine treatment, at a time when the edema had subsided, the "pustules" were involuting and the patients were well on the road to recovery. In case 13 anthrax bacilli recovered after the successful use of 400 cc. of serum showed on testing the same degree of virulence as the culture recovered before treatment was instituted.

#### TREATMENT

*Antianthrax Serum.*—This serum was administered to 18 patients (March 1933 to December 1938). Two additional patients received

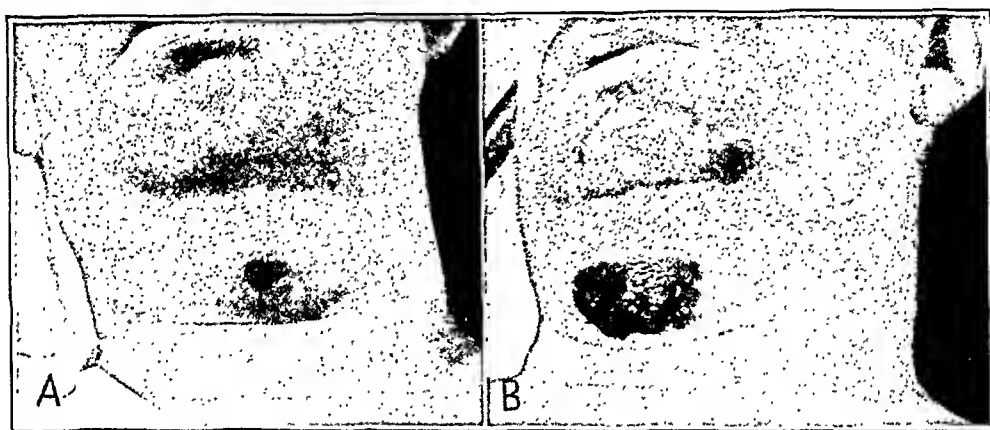


Fig. 5 (case 23).—*A*, appearance of the lesion when it was three days old. The anthrax papule is surrounded by a rectangular area of bluish erythema. Notice the marked edema of the soft tissues of the neck. *B*, the appearance of the lesion twenty-four hours later. Notice the extension of the black eschar, with vesiculation into the rectangular area of erythema. The edema is markedly increased in spite of medication with sulfapyridine and large doses of serum.

serum after a trial of sulfapyridine (1939 and 1940), and a third patient was treated with serum (1942) after he failed to respond to intensive sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) therapy. Most patients received serum early, on the second or the third day after the appearance of the papule. In 2 cases treatment was not given until five to six days had elapsed. Altogether serum can be credited with 20 recoveries and 1 death. In the first case encountered (1933) the patient died, and I believe that this death was due partly to the timorous use intravenously of insufficient quantities of antianthrax serum and partly to the injection of serum locally around the "pustule" as advocated by

Regan.<sup>2</sup> The latter procedure facilitated, rather than hindered, the spread of bacilli along tissue spaces that had been mechanically distended. My experience with the first 13 cases was reported in detail in two previous communications.<sup>3</sup> In general, I found antianthrax serum an effective and specific means of controlling anthrax edema and obtaining a cure. It was given in ample quantity (200 to 2,200 cc.), and each patient required an optimum dose, which could be administered in single or multiple injections. The intravenous route was found to be the most satisfactory. The claim of specificity is based on the clinical observation that the control of edema was accomplished in many cases only after a sufficient amount of serum had been given and without



Fig. 6 (case 14).—Anthrax of the forehead. The lesion is eight days old. The marginal vesicles have dried up and become part of the black eschar. The latter begins in the center of the "pustule" and spreads peripherally. Treatment was with antianthrax serum.

exhibition of the usual signs of nonspecific reaction to a foreign protein, such as fever and chill.<sup>4</sup> Excluding case 1, in which the patient died, I used a total of 17,490 cc. of antianthrax serum in treatment in 20

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2. Regan, J. C.: Treatment of Cutaneous Anthrax, *New York State J. Med.* **23**:113 (March) 1923.

3. Gold, H.: Studies on Anthrax: Clinical Report of Ten Human Cases, *J. Lab. & Clin. Med.* **21**:134 (Nov.) 1935; Cutaneous Anthrax, *Pennsylvania M. J.* **40**:728 (June) 1937.

4. The serum used was prepared at the Mulford Biological Laboratories. It is essentially an antibacterial serum of demonstrable protective value. "Normal horses are first immunized with subcutaneous injections of chemically killed anthrax

cases. The smallest total dose was 200 cc., and the largest was 2,200 cc., with an average total dose for the group of 874.5 cc. The smallest single intravenous injection of serum was 200 cc., while the largest was 1,000 cc. The smallest number of intravenous injections per case was one, while the largest was five. In most cases the optimum dose was administered in two to three injections. In the hope of maintaining the optimum concentration of serum I also gave large doses of serum intramuscularly in 7 cases, but this procedure was found to be too painful, and in 1 case (15) it produced a sterile abscess.

At first the period of serotherapy was prolonged in a vain attempt to cure the adenopathy, but I soon learned that control of the edema



Fig. 7 (case 31).—Anthrax of the hand. Note the small red papule and the surrounding edema of the ulnar half of the hand. Treatment was with sulfapyridine.

around the "pustule" was the most reliable yardstick to determine whether an optimum dose of serum had been given. When this dose was administered, the edema decreased rather promptly and disappeared

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bacilli and then hyperimmunized with increasing doses of highly virulent living organisms. After three months the serum from horses so treated agglutinates the anthrax strains used for immunization in a dilution of 1:2,500 or better. The serum contains precipitins, as demonstrated by the standard 4 plus polysaccharide-precipitin reaction it gives in a 1:10 dilution. It also contains protective antibodies, which are of special interest inasmuch as potent antianthrax serum injected in 5 cc. doses into full-grown sheep will afford appreciable protection against a virulent infective dose of anthrax bacilli for at least thirty days" (Sharp and Dohme: Personal communication to the author).



in eighteen to thirty-six hours. As collateral evidence of improvement I found that the temperature, pulse and white cell count returned to normal and that certain complaints, such as pain over the swollen lymph nodes and headache, also disappeared.

Most patients tolerated the large intravenous injections of serum well, but in cases 12 and 13 urticaria and angioneurotic edema developed, and in case 15 the patient suffered from severe intestinal cramps, back-ache, vomiting and thready pulse during the first injection of serum. Thermal reactions occurred frequently. Serum sickness developed in all

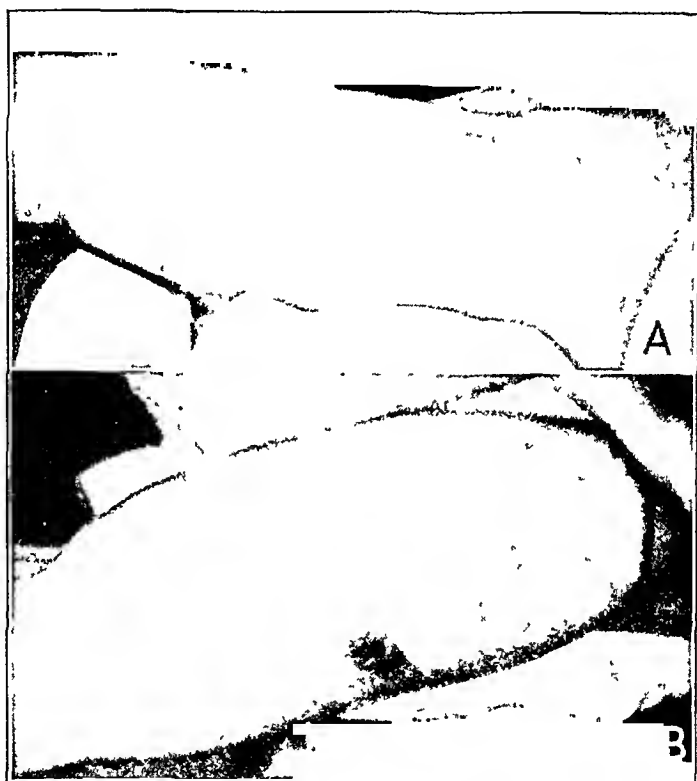


Fig. 8 (case 22).—*A*, normal right arm. *B*, anthrax of the left arm. The lesion was black and deeply ulcerated. Note the marked edema of the arm. Bright erythema of the skin over the swollen area was a conspicuous feature in this case. Treatment was with sulfapyridine.

cases, and in some it was rather severe. This is not surprising in view of the large amounts of unrefined serum injected. In all cases except case 1 the patients made a complete recovery after a rather troublesome convalescence. The average period of hospitalization in cases in which treatment was with serum was fifteen and three-tenths days; the average period of total disability was thirty-seven and five-tenths days (cases 23 and 55, in which the patients were treated with serum after they had failed to respond to sulfonamide compounds, are excluded).

*Neoarsphenamine*.—In addition to serum, intravenous injections of neoarsphenamine were given in 6 cases. A child of 10 (case 3) received 0.45, 0.6 and 0.6 Gm. on three successive days; 1 patient (case 2) received 0.6, 0.9 and 0.9 Gm. on the first, the second and the fourth day of treatment; 1 patient (case 4) received three daily doses of 0.9 Gm. each; 2 patients (cases 5 and 15) received two daily doses of 0.9 Gm. each, and 1 patient (case 23) received a single injection of 0.9 Gm. A comparative analysis of the records in these cases and the ones obtained in cases in which treatment was solely with antianthrax serum revealed that neoarsphenamine had not shortened the course of the disease or materially added to the chances of recovery; hence its routine use in addition to serum was discontinued after case 5 (1933). Later on (1937 and 1940) I again resorted to neoarsphenamine when the condition of 2 patients (cases 15 and 23) with anthrax of the forearm and the neck, respectively, became critical notwithstanding the administration of large doses of antianthrax serum. However, the injection of neoarsphenamine in these 2 cases was a gesture of despair, and it cannot be credited with the patients' recovery, since they were also given transfusions of blood from donors who had previously recovered from anthrax, as well as additional doses of serum.

*Sulfonamide Compounds*.—Sulfanilamide: In December 1938 I decided to try sulfanilamide therapy on a patient (case 19) with anthrax of the heel. I felt that the location of the lesion, the slight edema present and the absence of toxicity warranted the temporary withholding of serum. Large doses of sulfanilamide, 120 grains (7.8 Gm.) daily, were administered for three days, after which the daily dose was reduced to 90 grains (5.8 Gm.). The period of treatment lasted nine days, at the end of which time the edema had subsided and the lesion appeared as a dry black ulcer covered by a tough eschar. As a whole the effect of the drug was not spectacular, and although the patient recovered, I was not convinced that the sulfanilamide was responsible for the favorable results.

Sulfapyridine: Since October 1939 I have used sulfapyridine therapy in 24 cases of anthrax. In 18 of them this drug was used exclusively, with satisfactory results. In 4 cases I changed to sulfathiazole because of severe nausea and/or vomiting caused by the sulfapyridine. In all 4 cases the patients recovered, but in 1 case the cure should be credited to sulfapyridine, since the patient had received this drug for four days and the anthrax edema was well under control before a change to sulfathiazole was ordered. In 2 other cases antianthrax serum was resorted to. In case 26 (anthrax of the forehead, fig. 3 *A* and *B*) sulfapyridine therapy was stopped because of spreading edema, vomiting and restlessness after the patient had ingested 14 Gm. of the drug in forty-eight hours (the level of sulfapyridine in the blood was 13.5 mg. per hundred

cubic centimeters). She was then given three intravenous injections of serum, totaling 1,000 cc., with gratifying results (the patient was treated by Dr. Palmer de Furia). Although the cure in this case should be ascribed to serum, I believe in the light of subsequent experience that if chemotherapy had been continued for another twenty-four to forty-eight hours, it probably would have checked the edema. In the last case (23) a patient with anthrax of the neck failed to respond to sulfapyridine or its sodium salt. His condition became critical, but he recovered when treated with other means (details are given in the section headed "Immunotransfusion").

Of the 19 patients that responded to sulfapyridine, 9 were males and 10 were females. One was a Negro. All but 1 were adults, whose ages ranged from 18 to 50 years. The exception (case 28) was a girl of 12. The distribution of the lesions was as follows: the face, 4; the neck, 2; the arm, 3; the forearm, 1; the hand, 4, and the finger, 5. Thus, the lesion occurred on the face or neck in almost one third of the cases.

The initial dose of sulfapyridine was 2 to 4 Gm., followed by a dose of 1 Gm. every four hours. In some cases the drug was given every three hours, and a few patients received as much as 1.5 Gm. every three to four hours. The doses were repeated if vomiting occurred within one hour after ingestion of the drug. This schedule was maintained until the edema around the anthrax "pustule" receded. This took about two to five days. Thereafter, the dose was decreased gradually over a period of two to five days. The shortest period of treatment in the 18 cases in which cure was obtained by sulfapyridine alone was two days (anthrax of the finger). The longest period was ten days (anthrax of the face), and the average for the group was six and one-tenth days. In 50 per cent of the cases chemotherapy was stopped on the fifth day. In 3 cases treatment was perhaps unnecessarily continued beyond a week because of adenopathy in 2 cases and a secondary pyogenic infection of the ulcer in the third case. The smallest total dose of sulfapyridine was 15 Gm. (anthrax of the finger), while the largest dose was 45.5 Gm. (anthrax of the forearm). The average total dose for the group was 29.9 Gm. In this small series of cases there was no correlation between the location of the lesion, the duration of treatment and the amount of sulfapyridine given. Thus, in case 20 a patient with anthrax of the face was given 35.5 Gm. in ten days, while in case 41 a patient also with anthrax of the face was given 18.5 Gm. in five days. Likewise, in case 37, a patient with anthrax of the forearm received 45.5 Gm. in seven days, while in case 43 a patient with a "pustule" on the arm received 24 Gm. in five days. Since in all 4 cases treatment with sulfapyridine was started about two days after the appearance of the "pustule," the differences noted cannot be attributed to variation in the interval between the appearance of the lesion and the institution of therapy. It must be

remembered, however, that these comparisons are at best only suggestive, since no exact and precise rules governed the administration of the drug. In each case the patient was treated individually, and control of the edema was the guiding yardstick in determining dosage.

The interval between the appearance of the lesion and the time treatment was started was one day in 1 case, about two days in 8 cases, about three days in 4 cases, about four days in 2 cases, about five days in 2 cases and seven days in 1 case.

Slight to severe edema was present in all cases before chemotherapy was instituted. Actually, in 2 cases (21 and 35) treatment was withheld for twenty-four to thirty-six hours until edema appeared or became extensive. After the initial dose of sulfapyridine was given, the anthrax edema increased for about twelve to forty-eight hours; it then remained about the same for another twelve to forty-eight hours, after which it receded rather slowly, taking forty-eight to ninety-six hours for its disappearance.

Regional adenopathy occurred in all but 4 cases, and in some it developed a day or two after treatment was started. Usually the pain and tenderness over the nodes disappeared before the spread of the edema was checked. On the other hand, the adenopathy decreased in degree at a much slower rate than the edema and usually persisted throughout the illness even after the eschar was removed and the ulcer was clean and granulating. In 2 cases (24 and 31) the regional lymph nodes were palpable for more than a week after the ulcer had healed completely. In many cases the regional adenopathy was accompanied by swelling of the overlying soft tissues, which tended to disappear at a slower rate than the edema contiguous with the anthrax "pustule."

In 3 cases the patients had normal temperatures throughout their illness; in 11 cases the temperature ranged from 99 to 100 F. and in 5 cases from 101 to 102 F. before treatment was started. After administration of sulfapyridine the temperature returned to normal within twenty-four to seventy-six hours in all cases but 1. In the exceptional case (37) the patient showed a rise in temperature from 99.4 to 101 to 102 F. that started forty-eight hours after treatment was begun and lasted for two days. This fever was not due to the drug, since it disappeared without chemotherapy being stopped, but was associated with marked spread of the anthrax edema and the appearance of adenopathy. In many cases the temperature seemed to come down to normal before the edema was checked. However, the control of fever cannot be considered as reliable a yardstick of therapeutic efficacy as the control of edema.

The red cell count and the hemoglobin content were normal in the 11 cases in which the blood was examined. The total white cell count and the differential count were normal in 4 cases, while in the other 7 there was leukocytosis (9,050 to 12,800 cells), with a corresponding

increase in the neutrophils. In the few instances of leukocytosis the cell count when repeated about three days after treatment was started was found to have returned to normal.

The level of sulfapyridine in the blood was estimated in 13 cases, and the values ranged between 4 and 17.6 mg. per hundred cubic centimeters. In most cases the patients showed good blood levels (table 4).

The course of development and regression of the anthrax "pustule" did not seem to be affected by sulfapyridine.

TABLE 4.—*Blood Levels of Sulfapyridine in Relation to the Amount of the Compound Ingested for Treatment of Anthrax*

Case Number	Approximate Number of Hours of Treatment Before the Blood Level of the Drug Was Determined	Total Number of Grams of Sulfapyridine Ingested Before the Blood Level of the Drug Was Determined	Sulfapyridine in Blood, Mg./100 Cc.
20	62	18.0	17.6
22	12	8.5	10.4
	40	16.5	13.0
24	13	9.5	4.7
	37	20.0	9.0
	61	29.5	13.3
	'24,	....	1.4
	After Treatment Was Stopped		
25	24	7.0	4.0
	96	18.0	8.7
28	36	12.0	4.1
31	48	13.0	7.0
	120	27.5	0.0
34	64	17.0	9.5
36	48	12.0	11.1
41	60	15.0	6.1
30	48	15.0	8.0
35	48	17.0*	7.2
37	66	22.0	8.0
29	45	20.0	6.6

\* In this case the patient vomited in between doses during the first twenty-four hours.

In 11 cases the patients were hospitalized, and the average period of hospitalization was eight and five-tenths days. In the rest of the cases the patients were treated at home. The average period of disability for the entire group was seventeen and three-tenths days.

Reactions. In all cases the patients complained of marked nausea and loss of appetite. Occasional vomiting occurred in 4 cases. Because of gastric distress sulfapyridine therapy was stopped in 4 other cases. These complaints were not relieved by administration of alkalis or nicotinic acid. Drug fever occurred on 1 case (22). On the seventh day of treatment the temperature rose suddenly to 101 F. and stayed around 102 F. for forty-eight hours. Physical examination revealed nothing abnormal, and on laboratory examination the blood and urine appeared

normal. The anthrax infection was well under control and could not account for the fever, which disappeared soon after sulfapyridine therapy was stopped. In 1 case the patient complained of dysuria, but the urine was not abnormal. In case 24 hematuria developed on the third day of intensive therapy (29.5 Gm. of sulfapyridine was administered in sixty-one hours, and the blood level of the drug was 13.3 mg. per hundred cubic centimeters), but through a misunderstanding the administration of the drug was continued, and within twenty-four hours there was gross bleeding from the urethra. There was no dysuria, and the urinary output remained good. The blood pressure was 130 systolic and 80 diastolic, but the blood urea nitrogen was found to be 40 mg. per hundred cubic centimeters. Twenty-four hours after administration of the drug was stopped, the sulfapyridine content of the blood had dropped to 1.4 mg. per hundred cubic centimeters. Treatment consisted in forcing fluids and alkalis by mouth. The blood level of urea nitrogen and the urine returned to normal in four days. In case 23 there also developed renal pain, hematuria and slight elevation of the blood urea nitrogen, which cleared up in four days.

Sulfathiazole: In 16 cases treatment was with sulfathiazole. The patients' ages ranged from 3½ to 62 years. Most of them were between 18 and 43. Twelve were males, and 4 were females. In 4 cases the anthrax infection was initially treated with sulfapyridine, but the therapeutic agent had to be changed because of severe nausea and vomiting. In 3 of these 4 cases credit for recovery must be given to sulfathiazole. In 1 case (55) a patient aged 62 (anthrax of the neck) was treated for three days with large doses of sulfathiazole, without improvement. His condition became desperate, but the administration of 1,000 cc. of anti-anthrax serum followed in twenty-four hours by a second dose of 200 cc. resulted in recovery. Thus sulfathiazole can be credited with 14 recoveries and 1 failure. The location of the lesion was as follows: the face, 3 cases; the neck, 1 case; the arm, 1 case; the forearm, 4 cases; the hand, 1 case, and the finger, 5 cases.

Treatment consisted of an initial dose of 3 to 4 Gm. of sulfathiazole followed by a dose of 1 to 1.5 Gm. every three to four hours. In case 59 (anthrax of the arm) a child 3½ years old, weighing 30 lb. (14 Kg.), was given an initial dose of 1 Gm. followed by a dose of 0.5 Gm. every four hours for four doses. Thereafter, 0.25 Gm. of sulfathiazole was given every four hours. The largest total dose given was 56.6 Gm. in seven days (anthrax of the face), and the smallest total dose was 21.5 Gm. in five days (anthrax of the finger). In all cases but 1 treatment was begun early. In the exceptional case (45) the patient was kept under observation for six days before a papule on a finger developed the characteristics of anthrax, and on the appearance of edema, he was given sulfathiazole. The level of sulfathiazole in the blood was estimated

in 8 cases. In 4 the values were good, from 8 to 11.1 mg. per hundred cubic centimeters; while in the other 4 cases the concentrations were only 3.3 to 4.4 mg. per hundred cubic centimeters.

The spread of edema around the anthrax "pustule" was checked by sulfathiazole in one to four days after treatment was started; it then disappeared gradually, taking four to five days before the soft tissues returned to normal. It is my impression that sulfathiazole did not control the edema as promptly as sulfapyridine. Regional adenopathy was present in all cases. Case 33 (anthrax of the right cheek) was unusual in that a bilateral painful cervical adenopathy developed two days after treatment was started. The contralateral lymph node was actually larger, more painful and persisted over a longer period than the node on the right anterior cervical chain. There was an accompanying rise in temperature to 100.6 F. that lasted for thirty-six hours. Also in cases 46, 53, 54 and 60 (anthrax of the forearm, wrist, finger and forearm, respectively), in which the epitrochlear nodes were visibly enlarged, marked edema and redness of the soft tissues overlying the nodes developed after treatment with sulfathiazole was started. In case 46 there was a concomitant rise in temperature to 103 F. lasting for forty-eight hours. In 4 cases the regional nodes were visible and palpable for one to three weeks after the local lesion had healed.

In all cases but 3 the patients were treated at home. The average period of total disability for the group was twelve days.

Reactions. Slight nausea was present in most cases, but there was no vomiting. In 1 case (40) what appeared to be drug fever developed on the second day of sulfathiazole therapy. It disappeared within twelve hours after the drug was stopped. The only other reaction encountered was vertigo and a "feeling of being drunk" in 1 case (46). This disturbance of equilibrium occurred on the sixth day of treatment and cleared up completely about three days after administration of the drug was stopped.

Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine): Sulfadiazine was administered to 5 patients, 17 to 46 years of age. In case 48 (anthrax of the face) the total dose was 59 Gm. in eleven days; in cases 49 and 50 (anthrax of the forearm) the total doses were 34 Gm. in five days and 52 Gm. in seven days, respectively, and in case 51 (anthrax of the finger) the total dose was 25 Gm. in four days. In case 52 (anthrax of the neck), the total dose was 37 Gm. of sulfadiazine in three and twenty-five hundredths days and the edema, which had involved the anterior cervical space, was brought under control, but severe renal colic with gross hematuria developed. After a day's rest sulfathiazole was administered (1 Gm. every four hours), without any untoward reaction. Complete recovery ensued.

The initial dose was 3 to 4 Gm., followed by a dose of 1 to 1.5 Gm. every three to four hours. In cases 46 and 49 treatment was withheld for over twenty-four hours, until edema of the soft parts beyond the lesion had developed. Regional adenopathy and slight fever were also present. Good blood levels were obtained in all 5 cases, the values ranging from 15.4 to 23.5 mg. of sulfadiazine per hundred cubic centimeters. The sulfadiazine appeared to check the anthrax edema a bit more slowly than was the case with sulfapyridine or sulfathiazole, which accounts for the larger total dose and the more prolonged period of treatment. Hematuria was the only toxic reaction encountered. In all cases but 1 (52) the patients were treated at home. The average period of total disability for the group was seventeen and six-tenths days.

**Immunotransfusion.** It is not known whether recovery from anthrax confers any degree of permanent immunity to the disease, but instances of recurrent infection are rare. Smyth<sup>1</sup> reported several cases. Recovery appears to depend on local tissue immunity. Metchnikoff and Wright proved that phagocytosis is the essential process of recovery, and Besredka produced solid immunity in the guinea pig, which is the most sensitive animal known, without the development of humoral antibodies. On the other hand, the horse serum used in the treatment of anthrax contains agglutinins, precipitins and protective antibodies. Thus, the blood serum of the patient in case 10 gave a 4 plus agglutination reaction in a dilution of 1:64 and a 2 plus reaction in a dilution of 1:128 three days after the intravenous injection of 300 cc. of antianthrax horse serum. I attempted to determine the curative value of pooled convalescent serum in 1 case of anthrax. In case 18 (anthrax of the neck) the patient was given intravenously 375 cc. of pooled serum on the third day of illness, when edema was sharply circumscribed to an area the size of a small orange. The serum had been obtained from three patients about three months after they had recovered from anthrax, and it had been preserved in the frozen state for about three months before it was used. It did not prevent the spread of the edema, and twenty-seven hours after its injection I was obliged to administer 500 cc. of anti-anthrax horse serum, with gratifying results. In this instance the convalescent serum appeared to be of no value, either because of a low titer or because it was given in insufficient quantity. Yet 375 cc. constitutes a fairly large dose of serum.

Transfusions of whole blood obtained from donors that had recovered from anthrax were given in 2 cases. In case 15 (anthrax of the forearm, figs. 4 *A* and *B*) the patient failed to respond to two injections of serum, totaling 1,000 cc., and to sulfanilamide given by mouth, two tablets (5 grains [0.32 Gm.] each) four times a day for three days. The edema of the arm and the upper part of the chest increased; the skin around the elbow blistered and split; the temperature was 103 F., and the patient



was restless and toxic. She was then given 500 cc. of blood donated by a man who had recovered from anthrax about three and a half years before, followed by additional doses of 300 cc. of antianthrax horse serum and 0.9 Gm. of neoarsphenamine. Within six hours there occurred a startling change for the better. The patient fell asleep; the temperature dropped to normal, and the edema receded over the upper arm. Subsequently, she was given a second injection of neoarsphenamine and 200 cc. of horse serum intramuscularly, and she made a full recovery after a sterile abscess in the left buttock had been drained. The patient in case 23 was seen on Nov. 27, 1939, the second day after the appearance of a papule on his neck (figs. 5 *A* and *B* and 9). Because there was little edema, it was decided to withhold treatment for twenty-four hours. Next day he received 5.3 Gm. of sulfabenamidine (p-caproylamino-benzenesulfonhydroxamide). That evening the edema spread at an alarming rate, and the patient was placed on sulfapyridine therapy. In twelve hours he received 7.5 Gm. of the drug, but the blood level of sulfapyridine was reported as only 4.0 mg. per hundred cubic centimeters. After another dose by mouth (1.5 Gm.) the patient vomited repeatedly (blood in the vomitus), which necessitated discontinuance of oral therapy (November 29). He was then given 700 cc. of antianthrax serum, followed in twelve hours by a transfusion of 500 cc. of blood obtained from a donor that had recovered from anthrax twenty-one months before. Next day the edema spread across the anterior aspect of the upper portion of the chest and down to the level of the costal margin on the right side. Another 500 cc. of antianthrax serum was given, without any effect. On December 1, the sixth day of illness, the temperature was 102 F., signs of toxicity were increased and the skin on the neck was splitting because of the marked edema. Vomiting had subsided, and sulfapyridine therapy was resumed, with an initial dose of 3.5 Gm., followed by 1.5 Gm. every four hours. In addition, he received two intravenous injections of 5 Gm. each of sodium sulfapyridine eight hours apart. That night the edema had extended over the upper portion of the abdomen on the right side; 500 cc. of serum was given intravenously at 10 p. m. Next morning the blood level of sulfapyridine was reported as 9.1 mg. per hundred cubic centimeters. Repeated blood cultures were sterile, and the white cell count varied from 7,900 (82 per cent polymorphonuclear neutrophils) to 10,900 (84 per cent polymorphonuclear neutrophils). Adequate supportive therapy was ordered. On December 3, vomiting recurred and the patient complained of severe pain along the right ureter. Sulfapyridine therapy was stopped. The blood level of the drug was 4.1 mg. per hundred cubic centimeters. The urine showed a heavy cloud of albumin, numerous red cells and an occasional white cell. The edema had spread to the level of the right iliac crest, and the skin showed patchy cyanosis. The temperature was

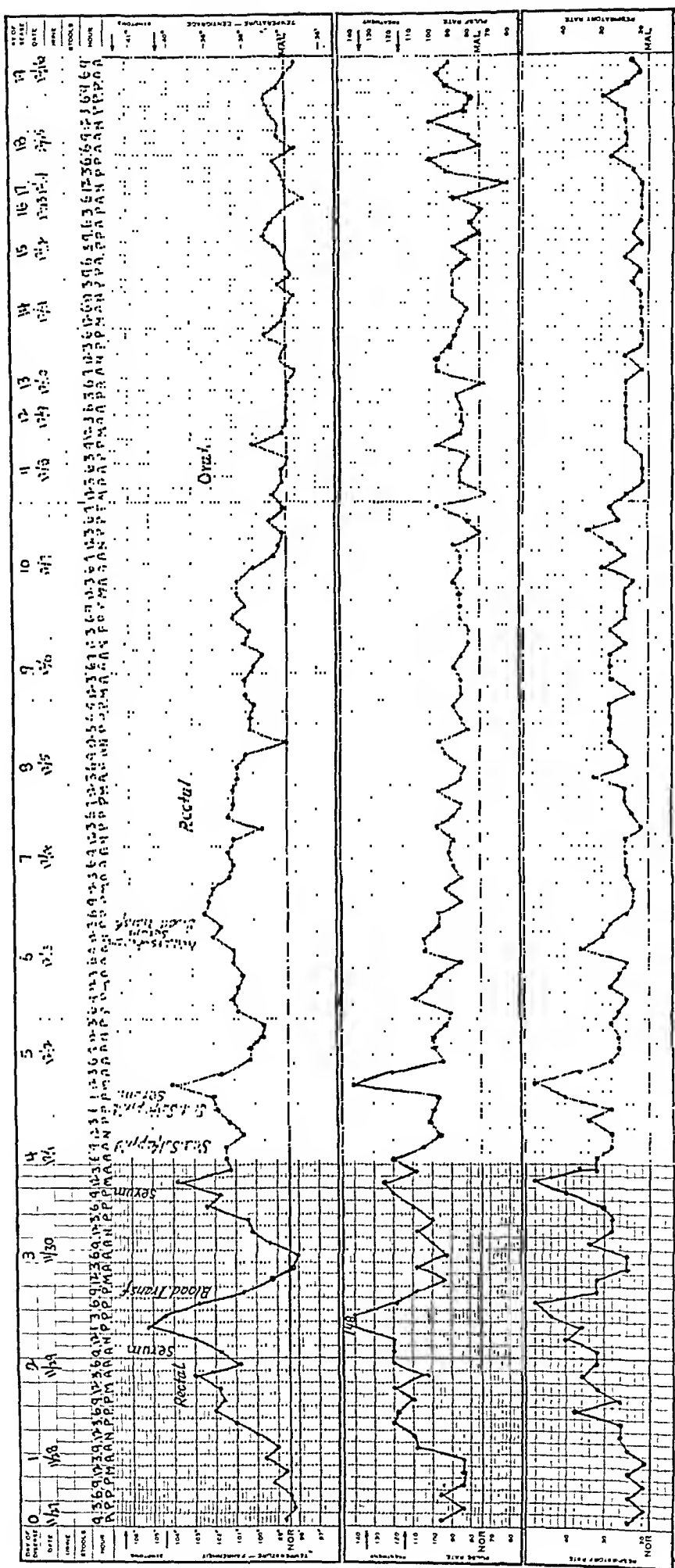


Fig. 9 (case 23).—Anthrax of the neck in a man aged 48. Treatment was with sulfapyridine, antianthrax serum, immunotransfusions and neoarsphenamine.

101 F., and the patient's condition was critical. Neoarsphenamine (0.9 Gm.) and serum (500 cc.) were given intravenously. Three hours later he received a second transfusion of 500 cc. of blood secured from a donor who had recovered from anthrax twenty-seven months before. Within three hours there occurred a dramatic change. The patient fell asleep; the temperature returned to normal; the swelling decreased over the lower portion of the chest on the right side so that the ribs could be outlined, and the erythema of the abdominal wall became much fainter. Thereafter, improvement was steady. On December 5 the blood level of urea nitrogen was found to be 38 mg. per hundred cubic centimeters, but it returned to normal three days later. The hematuria cleared up in four days. There was no change in the blood pressure.

In view of the multiple therapeutic approach employed, I am unable to credit recovery in these 2 cases to any particular agent. Yet I feel that the blood transfusions were of some value. It is likely, however, that blood from an ordinary donor, not one who has recovered from anthrax, would have been just as beneficial, especially since the first immunotransfusion in case 23 was ineffective and since attempts to demonstrate the presence of antibodies (agglutinins and precipitins) in convalescent serums obtained six months after the patients had been successfully treated with antianthrax horse serum or sulfapyridine proved to be unsuccessful.

#### COMMENT

The diagnosis of anthrax, though easy to make, especially if one is aware of its possible occurrence, should always be confirmed bacteriologically. The question of its prevention is a pressing public health problem, the importance of which can be gathered from the statement made by Smyth<sup>1</sup> that "if wool and hair had been disinfected as is done satisfactorily in England, there would have been saved some 33 lives and over 5,000 lost days." This problem can and should be managed by the government through the establishment of disinfecting stations at the ports of entry. England has found it worth her while — so would this country, but the chances that it will be done here in view of the present emergency and the decreasing mortality rate from anthrax are indeed remote. The best one can do now is to urge early recognition of the disease and prompt and adequate treatment. From 1934 to 1938 there were reported in the United States 375 cases of anthrax, with a fatality rate of more than 16 per cent, while in the previous five year period there were 379 cases, with a more than 22 per cent mortality. In individual series of cases in which treatment was careful, such as the one reported by Lucchesi and Gildersleeve,<sup>5</sup> deaths may not occur (no deaths in 67 cases), and after the first death in this series (inadequate treatment) I

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5. Lucchesi, P. F., and Gildersleeve, N.: Treatment of Anthrax, *J. A. M. A.* **116**:1506 (April 5) 1941.

handled 59 cases without a fatality. I agree with Lucchesi and Gildersleeve<sup>5</sup> that the excellent results obtained are due to the systemic treatment given while the local lesion is left strictly alone. There is no place in the modern therapeutics of anthrax for incision, excision or the injection of chemicals or serum into or around the lesion.

The value of antianthrax serum is now well established. It is essential that an adequate dose be given, and this varies with each patient, depending on the location of the lesion, the virulence of the organism and the time of treatment. From 200 to 500 cc. of serum should be given as an initial dose, to be repeated every twelve to twenty-four hours until edema is checked. Although recoveries have been reported in the European literature after the injection of small doses of serum,<sup>6</sup> it is important to emphasize that in my experience large amounts of serum are required in most cases of anthrax. This is in agreement with the observations of Lucchesi and Gildersleeve<sup>5</sup> in America and Batschwaroff in Bulgaria.<sup>7</sup>

I have found that control of the edema is the most reliable yardstick in determining whether sufficient serum has been administered in a given case. Contrary to the advice of Dumitresco and Jennesco,<sup>8</sup> I feel that the presence of adenopathy is no indication to continue serum treatment. The lymphoid enlargement may persist for days and weeks after the lesion has healed and the patient is on the road to complete recovery; it gradually disappears without any therapy.

The use of neoarsphenamine in the treatment of anthrax has been the subject of favorable reports by Hamilton,<sup>9</sup> Meschtschaninoff,<sup>10</sup> Spencer<sup>11</sup> and Gilbert.<sup>12</sup> Lucchesi and Gildersleeve<sup>5</sup> definitely expressed a preference for neoarsphenamine because it best fits the ideals for treatment, since it (1) does not harm the patient, (2) produces the lowest mortality rate, (3) causes the shortest absence from employment, (4) is the least expensive and (5) is easily given. However, these authors also stated that if a patient is afflicted with the internal type of anthrax, if the blood stream has been invaded or if the lesion is on the face or neck, serum

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6. Bodin, E.: The Treatment of Human Anthrax by Serotherapy, *Presse méd.* **35**:961 (Aug. 3) 1927.

7. Batschwaroff, W.: Anthrax in Bulgaria and Its Treatment with Immune Serum, *Deutsche med. Wchnschr.* **65**:1343 (Aug. 25) 1939.

8. Dumitresco, T., and Jennesco, C.: Antiserum Therapy of Anthrax, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:1360 (Nov. 7) 1932.

9. Hamilton, I.: Anthrax (Malignant Pustule) Treated by Anthrax Antiserum, with Note on Treatment by "Salvarsan" Preparation, *M. J. Australia* **1**:863 (June 18) 1932.

10. Meschtschaninoff, cited by Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

11. Spencer, H. A.: Human Anthrax: Its Effective Treatment with Organic Arsenic Preparations, *J. Trop. Med.* **37**:9 (Jan. 1) 1934.

12. Gilbert, F. W.: Human Anthrax in Barotesland Treated with Novarsenobenzene (Neoarsphenamine), *Lancet* **2**:1283 (Dec. 7) 1935.

is the agent of choice. Lucchesi and Gildersleeve added that if there is any doubt as to the type of treatment desired, serum should be administered. Published reports on the value of nearsphenamine in the treatment of experimental anthrax in animals<sup>13</sup> are not encouraging. Likewise, Eurich,<sup>14</sup> using both serum and arsphenamine in treatment in 200 cases of cutaneous anthrax, with a mortality rate of 5 per cent, found that the relative value of the two substances was uncertain. In my hands nearsphenamine did not prove to be of much value when given in addition to serum in a small group of cases. Lovett,<sup>15</sup> of the Municipal Hospital for Contagious Diseases, Camden, N. J., has expressed a similar opinion.

Several reports have been published on the use of sulfonamide compounds in the treatment of anthrax. Ivanovics<sup>13c</sup> found that sulfanilamide, sulfapyridine and sulfoglycoside (4,4''-diaminodiphenylsulfoglycoside) had little or no influence on the course of infection in mice when given immediately after inoculation with a strain of anthrax bacilli of constant virulence. On the other hand, Cruickshank<sup>13d</sup> stated that of the agents tested only sulfapyridine and sulfanilamide were found to have beneficial action on the course of anthrax infection in mice, and of the two, sulfapyridine was more effective in delaying death in the infected animals. When large doses of sulfapyridine were given, a considerable proportion of the mice survived and the curative effect was complete in the sense that the organism was not recoverable from the tissues of the mice. In all experiments but the last all or almost all of the control mice died. In the last experiment, with a death rate of 80 per cent among the controls, the death rate among the mice treated with sulfapyridine was reduced to 33.3 per cent. Moreover, it seems that sulfapyridine has in the mouse a far more effective action than arsenical compounds. Similarly, May and Buck<sup>16</sup> reported that sulfapyridine and to a less extent sulfanilamide and sulfoglycoside delay death in mice infected with fully virulent encapsulated non-spore-forming anthrax bacilli, although no ultimate decrease in mortality results from using these drugs. The results suggest that sulfapyridine had the effect of temporarily holding up the course of infection. In comparative experi-

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13. (a) Urbain, A.; Théobalt, E., and Vallée, M.: A Study on the Chemotherapy of Experimental Anthrax Infection in Laboratory Animals, *Compt. rend. Soc. de biol.* **104**:1204, 1930. (b) Kurotchkin, T. J., and Reimann, H. A.: Comparative Values of Antianthrax Serum and of Neosalvarsan in Treatment of Experimental Anthrax, *J. Infect. Dis.* **46**:36 (Jan.) 1930. (c) Ivanovics, G.: Effect of Sulfanilamide and Similar Preparations on Anthrax, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **96**:252 (Aug. 31) 1939. (d) Cruickshank, J. C.: Chemotherapy of Experimental Anthrax Infection, *Lancet* **2**:681 (Sept. 23) 1939.

14. Eurich, F. W.: Some Notes on Industrial Anthrax: Its Diagnosis and Treatment, *Brit. M. J.* **2**:50 (July 8) 1933.

15. Lovett, J. C.: Personal communication to the author.

16. May, H. B., and Buck, S. C.: Action of Sulphonamides in Experimental Anthrax, *Lancet* **2**:685 (Sept. 23) 1939.

ments with two commercial serums May found that there was no difference at any stage of the experiments between treated and control animals; similar results have also been obtained by Tomcsik and Ivanovics<sup>17</sup> with serums commercially available in Hungary. However, a special serum prepared in rabbits saved 9 of 12 mice. May also reported that the results obtained by using antianthrax rabbit serum together with sulfapyridine were no better than those obtained with serum alone. May stated that it by no means follows that a serum conferring no protection on the mouse would be valueless in the treatment of anthrax in human beings. While these experiments were being carried out, 2 patients with severe cutaneous anthrax were treated by May with sulfapyridine and Sclavo's antianthrax serum. The author stated that while both patients recovered, it cannot justifiably be claimed that the use of the drug played any material part in overcoming the infection. In the series reported by Lucchesi and Gildersleeve<sup>5</sup> sulfanilamide was given in 3 cases. In 2 cases patients had been given the drug before admission for one and four days with total doses of 60 grains (3.9 Gm.) and 250 grains (16.2 Gm.), respectively. In both cases it was necessary to use serum after admission. In a third case the patient was treated with sulfanilamide alone, but the lesion involuted slowly, and he was confined to the hospital for twenty-four days, with a culture of material from the lesion positive for anthrax bacilli on the twentieth day of hospitalization. The authors' clinical impression was that these patients did not fare as well as their other patients. Ferenczi<sup>18</sup> treated 4 patients with anthrax with sulfanilamide (deseptyl) and stated:

The first patient, with severe anthrax of the forearm, was cured with one injection of the drug and two tablets given by mouth three times a day. The second patient, with a lesion on the forearm, was handled in the same way as the first one. The third patient, with a lesion on the neck and severe swelling, was given 20 cc. of serum, without improvement. The next day 10 cc. of sulfanilamide was administered intravenously, and two tablets of the drug were ordered three times a day. The fever fell in forty-eight hours, and the patient recovered. The fourth patient, with multiple lesions (5) on the forearm, recovered shortly after chemotherapy was started.

Dorffel<sup>19</sup> reported 2 cases of anthrax in which treatment with prontosil (the hydrochloride of 4-sulfamido-2'-4'-diaminoazobenzene) was successful. In the first case the patient received two tablets three times daily; her temperature returned to normal on the fourth day, and the inflammatory process subsided before 40 cc. of serum was injected. A second dose of serum was injected six days later. It is not clear

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17. Tomcsik, J., and Ivanovics, G.: Immunizing Action of Anticapsular Immune Body in Anthrax, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **94**:28 (Oct. 5) 1938.

18. Ferenczi, A.: New Therapy of Anthrax, *Deutsche med. Wchnschr.* **66**:435 (April 19) 1940.

19. Dorffel, J.: Neoprontosil in the Therapy of Anthrax, *Deutsche med. Wchnschr.* **66**:827 (July 26) 1940.

from the report why serum was given after improvement had set in. In the second case, in which the author designated the illness as pseudo-anthrax, the patient recovered after two weekly courses of chemotherapy (two tablets three times a day—with eight days between the courses). Ravina<sup>20</sup> reviewed 2 cases reported by Chanial in which anthrax was treated with serum and sulfanilamide (1 case) and with sulfapyridine (1 case) and stated that fever and edema subsided abruptly after the administration of the compounds. Ravina also referred to the work of the Rumanian physicians, Munteanu and Zeltzman, who treated 8 patients with anthrax, 5 of whom were severely ill, with N<sup>4</sup>-benzylsulfanilamide (46 RP) administered by mouth, in addition to injections of the same sulfanilamide derivative, with recovery of all patients in six to ten days. Eight control patients were treated with large doses of serum; 3 died and 5 recovered, the latter taking thirty-eight days to get well. Finally, Ravina mentioned a patient with severe anthrax treated by Brimont with sulfapyridine given by mouth and a 5 per cent ointment of sulfanilamide applied locally. The boy recovered after three days of treatment. Ravina concluded that a sulfonamide compound alone or in association with serum cures anthrax. Bonnar<sup>21</sup> reported 2 cases of anthrax in human beings in which treatment was with sulfapyridine. Recovery cannot, however, be credited to this drug, since in both cases the patients had previously received two doses of Sclavo's antianthrax serum and of neoarsphenamine, and improvement followed too soon after the sulfapyridine therapy was started. Recently, Davidson<sup>22</sup> reported a case in which anthrax of the neck was cured by arsenicals and sulfapyridine. The patient received a full course of sulfapyridine therapy, with 2 Gm. as an initial dose, followed by 1 Gm. every four hours for forty-eight hours and then 1 Gm. three times a day for thirty-six hours. Later he was given 0.5 Gm. twice a day for four days, making a total dose of 24.5 Gm. On the day after admission to the hospital 10 cc. of Sclavo's antianthrax serum was given subcutaneously. Arsenic was also given, intravenously, in the form of neoarsphenamine in a dose of 0.6 Gm. on the second, the third and the sixth day after admission. Davidson credited the cure to the chemical agents used, since Sclavo's serum can be disregarded on account of the small quantity given.

I have used sulfonamide compounds in treatment in 42 cases, with excellent results in 39. In 1 case (26), sulfapyridine was discontinued too soon and serum was given instead; in 2 cases (23 and 55) the patients were treated intensively with sulfapyridine and sulfathiazole, respectively, but they failed to respond to these drugs. Judging by the

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20. Ravina, A.: Treatment of Anthrax by Sulfonamide Compounds, *Presse méd.* 48:424 (April 17) 1940.

21. Bonnar, W.: Sulphapyridine in Human Anthrax, *Brit. M. J.* 1:389 (March 9) 1940.

22. Davidson, I. M.: Cutaneous Anthrax Treated by Arsenicals and Sulfapyridine, *Brit. M. J.* 2:725 (Nov. 22) 1941.

speed with which anthrax edema was controlled, I found sulfapyridine to be the most effective (one to three days); next came sulfathiazole (one to four days), then sulfadiazine (two to five days) and lastly sulfanilamide (five days?). However, the greater efficacy of sulfapyridine is partly overcome by the greater incidence of reactions, especially nausea, vomiting and hematuria, that it produces. Therefore, at the present time I consider sulfathiazole the drug of choice. The following procedure was adopted: After the diagnosis of anthrax is made, large doses of sulfathiazole are given for two to three days, with frequent checking on the urine, the blood count and the concentration of the drug in the blood. If the edema is not controlled by the third day, large doses of antianthrax serum are resorted to. If the spread of the edema is checked by sulfathiazole, chemotherapy is continued until the edema disappears.

The period of illness is definitely shortened by this form of chemotherapy. While the average period of hospitalization was fifteen and three-tenths days in the cases in which treatment was with serum, it was eight and five-tenths days in the cases in which treatment was with sulfapyridine. An even more striking difference was noted in the number of work days lost. Thus, the average period of total disability in the former group was thirty-seven and five-tenths days, while in the cases in which treatment was with a sulfonamide compound (sulfapyridine, sulfathiazole or sulfadiazine) it was fifteen and four-tenths days. In addition, chemotherapy enabled me to keep many patients at home, thus saving on hospital beds as well as expense. It does not produce the unpleasant reactions associated with serum therapy (thermal reaction, anaphylactic reaction and serum sickness) and does not sensitize the patient to a foreign protein. Finally, it has the great advantage of simplicity of administration. At my suggestion Lovett<sup>15</sup> treated 3 patients with sulfathiazole. He reported:

The first one had been sick for four days, and he was given sulfathiazole and 500 cc. of serum, which compared favorably with the doses of 900 to 1,100 cc. that were used on 4 patients with anthrax previously treated with neoarsphenamine. The second patient recovered under sulfathiazole therapy alone. The third patient, ill five days, was toxic and edematous. The lesion was located on the right upper eyelid. He recovered after receiving sulfathiazole and 1,100 cc. of serum. This is 1 patient I felt sure would die, so I believe that the sulfathiazole was of great benefit.

My experience to date indicates that sulfonamide compounds are a reliable and safe substitute for serum in the therapy of anthrax and should be given preference in the treatment of this disease.

#### SUMMARY AND CONCLUSIONS

Sixty cases of anthrax are reviewed. Sources of infection, yearly occurrence, distribution, clinical course and methods of treatment are discussed.



In 21 cases treatment was with antianthrax serum. One death occurred. To secure recovery large amounts of serum (200 to 2,200 cc.) were administered intravenously. In each case an optimum dose sufficient to control the edema was required.

Neoarsphenamine given in addition to serum was found to be of little or no benefit.

In 42 cases of anthrax treatment was with sulfonamide compounds, with excellent results in 39 cases. In 1 case (23) the patient became worse after intensive treatment with sulfapyridine and its sodium salt, but he recovered after the injection of large doses of antianthrax serum and neoarsphenamine and immunotransfusions. In case 55 the patient failed to respond to adequate doses of sulfathiazole, but he recovered after the administration of serum. In the remaining case (26), sulfapyridine therapy was stopped too soon and antianthrax serum was given instead, with good results.

Sulfapyridine was found to be the most effective sulfonamide compound; next came sulfathiazole, then sulfadiazine. However, because of the high incidence of nausea and vomiting encountered in the course of sulfapyridine therapy, I consider sulfathiazole the drug of choice at the present time.

Large doses of sulfathiazole should be given until edema is controlled. If a patient fails to respond after three days of treatment, antianthrax serum should be resorted to.

Sulfonamide compounds are a safe and reliable substitute for antianthrax serum. These chemotherapeutic agents are easy to administer; their use materially shortens the period of hospitalization and disability, and they are economical.

#### REPORT OF NINE CASES

CASE 21.—On Feb. 10, 1939 W. N., a white man aged 23, scratched the left side of the neck with a wire, while attempting to lift a roller in the carding room. The wound was painted with tincture of iodine. On the night of February 12 the neck itched a little, and on February 13 there was a "sore" at the site of the scratch. He came to the office on the next day when a dry black "pustule" was discovered just below the middle of the left half of the jaw. A small area of edema, the size of a quarter, surrounded the papule, and a small tender lymph node, the size of a marble, was palpable below the left cricoid cartilage. The patient was admitted to the Chester Hospital, where the diagnosis of anthrax was confirmed bacteriologically. On February 15 the edema spread over the entire anterior cervical triangle on the left side, and a second node was palpable on the posterior cervical chain above the clavicle. There was no fever. The white cell count was 11,200, with 87 per cent polymorphonuclear neutrophils. The urine was normal. The patient was then given a dose of 3 Gm. of sulfapyridine, followed by a dose of 1 Gm. every four hours. Next day the edema remained unchanged, but on February 17 a definite decrease in the swelling was noted. The two lymph nodes were also smaller. On February 18 the neck had a normal contour. The lesion was depressed and dry. The white cell count was 5,400, with 61 per cent polymorphonuclear neutrophils. The dose of sulfapyridine was reduced to 1 Gm.

every six hours. On February 20 the eschar was removed, leaving a superficial ulcer with a purulent base. Sulfapyridine was decreased to 0.5 Gm. every six hours. On February 21 the ulcer was granulating, the adenopathy was much less extensive and the patient was discharged from the hospital. The intake of sulfapyridine was 28.5 Gm. in five and five-tenths days. The patient was declared cured on February 25. Total disability lasted twelve days.

CASE 36.—On Dec. 11, 1940 R. S., a white woman aged 23, noted a "small pimple" on the right arm just above the elbow. When seen the next morning she showed an anthrax "pustule," with swelling of soft tissue both above and below the right elbow; her temperature was 99.2 F. She was admitted to the Chester Hospital,

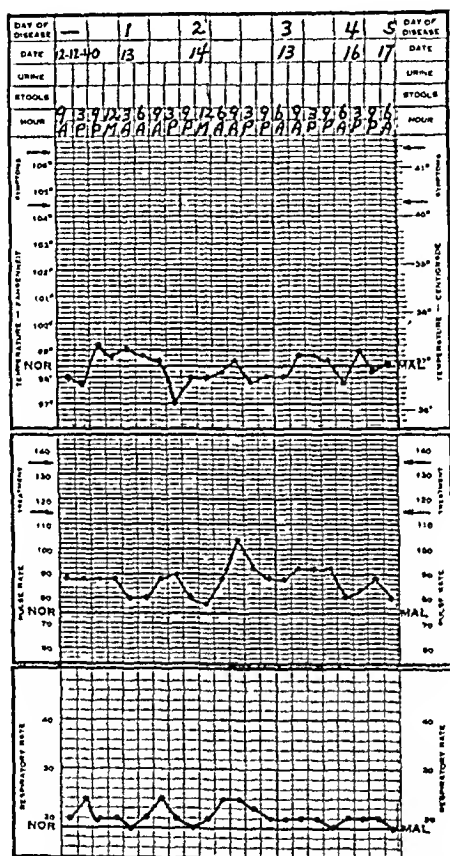


Fig. 10 (case 36).—Anthrax of the arm in a woman aged 23. Treatment was with sulfapyridine.

where the diagnosis of anthrax was confirmed bacteriologically (fig. 10). She was then given 2 Gm. of sulfapyridine; the dose was repeated in four hours and was followed by a dose of 1 Gm. every four hours. The white cell count was 8,800, with 83 per cent polymorphonuclear neutrophils. On December 13, the temperature became normal and the edema disappeared, but the skin around the "pustule" became bright red, and the right axilla was painful. On December 14 the lesion had a button-like appearance and was dry. The cutaneous erythema, though pale, had spread upward, and the axillary node was vaguely outlined and was slightly tender. The patient complained of marked nausea but did not vomit. The blood level of sulfapyridine was 11.1 mg. per hundred cubic centimeters. The dose was reduced

to 0.5 Gm. every four hours. On December 16 she felt much improved; the lesion had a black center, the peripheral vesicles were dry and wrinkled and the adenopathy and erythema had disappeared. Sulfapyridine was ordered every six hours. The patient was sent home on December 17. The total intake of sulfapyridine was 23 Gm. in five days. The eschar was removed a few days later, and she was declared cured on December 26. Total disability lasted fourteen days.

CASE 32.—On Aug. 9, 1940 E. K., a white man aged 19, noted a small pimple below the right eye, which he painted with tincture of iodine. He continued to work until August 12, when he was sent to my office because of swelling of the face. Examination revealed a lesion below the right infraorbital ridge that resembled a flea bite, with edema around it covering an area the size of a quarter. There were two palpable lymph nodes, one at the angle of the jaw and the other at the upper end of the anterior cervical chain on the right side. The temperature was 99.4 F. A smear and a culture of material from the lesion were positive for anthrax bacilli. The patient was treated at home. The initial dose of sulfapyridine was 3 Gm., followed by a dose of 1 Gm. every four hours. Next day, the lesion was more typical in its appearance and there was an increase in the edema below the right eye. There was also swelling of the soft tissues overlying the lymph node at the angle of the jaw. On August 14 the temperature was normal, but the edema had spread around the external canthus. The lesion was moist; the patient appeared to be depressed, had vomited throughout the night and refused to go on with oral therapy. A sample of blood taken two hours after the last morning dose (none during the night) showed 3.5 mg. of sulfapyridine per hundred cubic centimeters. He was then placed on sulfathiazole therapy, 1 Gm. every four hours. On August 15, the swelling had increased and the eye was half closed. The lymph nodes were larger, and the lesion was oozing freely. One and five-tenths grams of sulfathiazole was ordered every three hours. There was neither nausea nor vomiting. The fluid intake was excellent. On August 16 the edema of the face had spread down to the level of the mouth and upward along the zygoma. The right eye could be opened only one third of the way, and the skin over the bridge of the nose was bright red. A sample of blood taken two and one-half hours after the last dose showed 8.0 mg. of sulfathiazole per hundred cubic centimeters. The dose was then reduced to 1 Gm. every three hours, and I decided to resort to antianthrax serum if the spread of the edema was not checked within twelve hours. That evening there was some decrease in the swelling of the lower part of the face, and the eye was more widely opened. On August 17 there was definite decrease in the edema. The lesion was covered by a dry black eschar. Sulfathiazole was administered every four hours until August 16, when the dose was reduced to 1 Gm. every six hours. There was steady improvement, and on August 22 the eschar came off, leaving a small ulcer that healed completely by August 31. The lymph nodes remained palpable for another two weeks. The total sulfathiazole intake was 43 Gm. in seven days. Total disability lasted fourteen days.

CASE 33.—On Aug. 22, 1940 F. K., a white man aged 19, noticed on the right cheek a pimple that itched a little. Examination revealed a red papule, the size of a nickel, with a yellow, excoriated top. Edema of the face developed a few hours later. There was neither adenopathy nor fever. A smear and a culture of material from the lesion were positive for anthrax bacilli. The patient was treated at home. The initial dose of sulfathiazole was 3 Gm., followed by a dose of 1.5 Gm. every four hours. On August 24 the lesion looked like a flat button with an ulcerated center

and a red rim. The cheek appeared to be more swollen, and a small tender node had appeared at the right angle of the jaw. A sample of blood taken three hours after the morning dose showed only 1.8 mg. of sulfathiazole per hundred cubic centimeters. The same night the patient complained of pain on both sides of the neck and across the back. He was covered with sweat, and the temperature had risen to 100.6 F. The edema of the face was increased, and an additional node was palpable bilaterally in the middle portion of the neck (anterior chain). The node on the left side was larger and more tender. Sulfathiazole was increased to 1.5 Gm. every three hours. The temperature and the pain subsided the next day (August 25), but the three lymph nodes were still palpable and tender. The edema of the face began to subside late at night. A sample of the blood taken on August 26 contained only 3.3 mg. of sulfathiazole per hundred cubic centimeters, in spite of intensive therapy which was well tolerated. On August 27, the temperature was normal, the face was less swollen and the nodes were less tender. The lesion was black and oozing. On August 29, the lower half of the face was still somewhat swollen, but the lymph node on the right side was hardly palpable; the contralateral node was the size of a marble, though not tender. One gram of sulfathiazole was ordered every four hours. The eschar began to separate at the edges on August 31 and came off four days later. The ulcer was completely healed on September 9, but the pealike lymph nodule was palpable on the left side of the neck for two weeks. The total intake of sulfathiazole was 56.5 Gm. in seven days. Total disability lasted eighteen days.

CASE 40.—On March 9, 1941 C. W., a white woman aged 25, noted a "small pimple" on the left side of her chin. Next day it itched a little and began to swell. When examined on March 11 at 7 p. m. the lesion consisted of a small papule with a vesicular top and an ulcerated center. Surrounding it was a ring of erythema and edema that spread to the submental area. The left submental lymph node was the size of a walnut. There was also a node at the upper end of the right posterior cervical chain. Her temperature was 100 F. A smear and a culture of material from the lesion were loaded with anthrax bacilli. She was treated at home. The initial dose of sulfapyridine was 3 Gm. In the next twelve hours she took 3 Gm. of the drug, and because of a misunderstanding of instructions to repeat the dose if vomiting occurred within one hour after taking the sulfapyridine, she ingested 6 Gm. in the following four hours. The severe vomiting that ensued produced marked dehydration and forced a change in treatment. On March 13 she was given 2 Gm. of sulfathiazole followed by 1 Gm. every four hours. At 10 a. m. the temperature was 98.8 F. The lesion had enlarged considerably and was moist; the chin and the lower part of the face were markedly swollen. At 8:30 p. m. the temperature was 100 F. Sulfathiazole was ordered every three hours. On March 14 the blood level of sulfathiazole was 9.7 mg. per hundred cubic centimeters. The swelling was unchanged. At 8 p. m., the temperature jumped to 103 F. and the pulse rate was 118 per minute. There were no complaints, and physical examination revealed nothing abnormal. Next morning, the temperature was 101.6 F. and there was definite decrease of the swelling of the face, although the submental area was prominent, because of enlargement of the regional node (left). The right cervical node was much smaller. Because of the possibility of drug fever the medication was stopped. The total intake of sulfathiazole was 16 Gm. in two days. On March 15, the temperature returned to normal and the edema of the chin was lessened. Thereafter, improvement was steady. The eschar was removed on March 24, leaving a flat ulcer with a clean base

that healed in four days. However, the bulge under the chin, due to the enlarged lymph node, was still prominent as late as April 8 and did not disappear for another two weeks. Total disability lasted eighteen days.

CASE 49.—J. D., a white man aged 20, was well until the night of Aug. 14, 1941, when he felt some pain in the left axilla. Looking around he found a "small pimple" on the external surface of the left forearm below the elbow. When seen in the office on August 15 he had a typical anthrax "pustule" on the forearm, with some edema around it. A lymph node the size of a walnut was palpated in the left axilla. The temperature was 98.8 F. A smear and a culture of material from the lesion were positive for anthrax bacilli. Because of the small amount of edema present it was decided to postpone treatment. The patient was kept at home and was given sodium bicarbonate tablets as substitute therapy. On March 16, the lesion was brown and the swelling had definitely increased, involving the outer half of the upper third of the forearm. Four grams of sulfadiazine was then given as an initial dose, followed by a dose of 1 Gm. every four hours. Next day, the edema was increased and the skin on the external surface of the upper half of the forearm and the lower third of the arm was bright red and hot to the touch. The axillary node was unchanged. There was no fever. On March 18 the edema involved the entire upper half of the forearm, but the cutaneous erythema was lessened and the lymph node was smaller and not as tender. The lesion was black and moist. The dose of sulfadiazine was increased to 1.5 Gm. every four hours. On March 19 the blood level of sulfadiazine was 15.4 mg. per hundred cubic centimeters. The edema of the forearm showed no change, but the erythema had decreased considerably. The dose was reduced to 1 Gm. every four hours. That evening the swelling of the arm began to decrease. This was more definite on the following morning, when the dose was reduced to 0.5 Gm. every four hours. On March 21 the edema had disappeared except for a small area around the lesion, which was black and dry. Sulfadiazine was stopped after an intake of 34 Gm. in five days. The eschar was removed on March 25, leaving a deep ulcer that healed in a week. Total disability lasted eighteen days.

CASE 52.—D. L., a white man aged 46, worked as a carder until Dec. 18, 1941, when he came to the office because of a "sore" on the back of the neck (right side). There was no history of trauma. On December 15 he had noticed a small "pimple" on the neck, which, though painless, had gradually increased in size. Examination revealed a typical anthrax lesion with slight edema of the surrounding tissues. There was no adenopathy. At 12 noon his temperature was 99.6 F. A smear and a culture of material from the lesion were positive for anthrax bacilli. He was given 4 Gm. of sulfadiazine followed by a dose of 1.5 Gm. every four hours.

Next morning the patient was seen at home, when he appeared to be distressed and complained of headache, pain in the abdomen and fever. The temperature was 101 F. The swelling around the lesion had increased considerably; there were firm induration of the right half of the back of the neck and loose edema below the right ear and the angle of the jaw. The patient was then admitted to the Chester Hospital (fig. 11). At 1 p. m. his blood level of sulfadiazine was 13 mg. per hundred cubic centimeters. One and five-tenths grams was ordered every three hours. On December 20 the patient was feverish and complained of pain in the epigastrium. The lesion was black with large peripheral vesicles, and the edema had spread upward into the scalp, across the back of the entire neck and forward into the right anterior cervical space. There was also hard induration in front of and below the

right ear. On examination the urine was acid, had a specific gravity of 1.016 and contained a faint trace of albumin, a few epithelial cells and many calcium sulfate and sulfadiazine crystals. A blood count showed 5,330,000 red cells, a hemoglobin content of 15 Gm. per hundred cubic centimeters (93 per cent) and 13,500 white cells, of which 91 per cent were polymorphonuclear neutrophils (58 per cent band forms and 33 per cent segmented forms), 1 per cent were basophils and 8 per cent were lymphocytes. At 9 p. m., the patient complained of pain across the left side of the back, the edema had obliterated the cervical and the supraclavicular space on the right side and the skin over this area was bright red.

On December 21 the patient was restless and was suffering from typical renal colic (left side). There was gross hematuria, and a specimen of urine was loaded

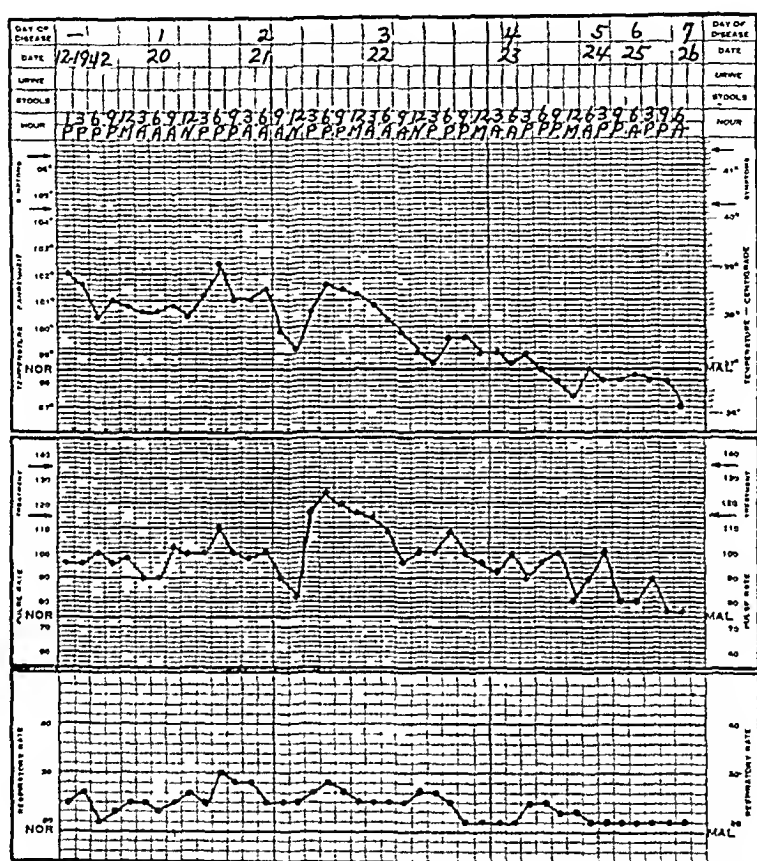


Fig. 11 (case 52).—Anthrax of the neck in a man aged 46. Treatment was with sulfadiazine and sulfathiazole.

with mucous shreds and sulfadiazine crystals. He had vomited three times during the morning. The last dose of sulfadiazine had been given at 12 noon. At 11 a. m. (two hours after medication) his blood level of sulfadiazine had been 16 mg. per hundred cubic centimeters. The swelling and the induration of the back of the neck and face had decreased a little, but the loose edema of the anterior cervical area had increased somewhat. Morphine, alkalis by mouth and an intravenous injection of 1,000 cc. of 10 per cent dextrose in physiologic solution of sodium chloride were given. At 8 p. m. the temperature was 101.6 F.; the pain and tenderness over the left loin had lessened, but the edema had spread down over the manubrium. Erythema of the skin over the area of spreading edema was a striking feature.

On December 22, the patient was less toxic and the renal pain had subsided. The output of urine was decreased; the blood pressure was 130 systolic and 78 diastolic, and the blood level of urea nitrogen was 16 mg. per hundred cubic centimeters. The spread of the edema had halted, and the patient seemed improved. Twenty-one hours after chemotherapy had been stopped the blood level of sulfadiazine was still 13 mg. per hundred cubic centimeters. At 6:30 p. m. the temperature was down to 99.6 F. There was an occasional pain over the suprapubic area, but the urine was grossly clear of blood. The edema of the neck was definitely lessened. At 10 a. m. 1 Gm. of sulfathiazole was ordered every four hours. On December 23 the patient was much improved and the area of induration in front of and below the right ear was much softer. The edema of the neck was decreased. Next day a dry black eschar developed on the lesion. Sulfathiazole was given every six hours. On December 26 the neck had a normal contour and the lesion was dry and black, with a surrounding area of induration the size of a silver dollar. Five tenths of a gram of sulfathiazole was ordered every six hours. The urine was still acid and contained a trace of albumin, 10 to 12 white cells per high power field and an occasional epithelial cell but no red cells. The patient was sent home on December 27. Five tenths of a gram of sulfathiazole four times a day was ordered for two days. The area of induration and the eschar, which had appeared rather late, persisted for over three weeks. The patient returned to work on Jan. 14, 1942, but the ulcer was deeply infected (staphylococci) and responded slowly to local treatment. He was discharged cured on Feb. 7, 1942. The total intake of sulfadiazine was 37 Gm. in three and twenty-five hundredths days. The total intake of sulfathiazole was 25.5 Gm. in seven days. Total disability lasted twenty days.

CASE 55.—L. M., an obese white man aged 62, worked as a carder until March 2, 1942, when he came to the office with a typical anthrax lesion on the right side of the neck below the angle of the jaw. A large edematous area surrounded the "pustule." The next day, it turned red and the neck became swollen. The temperature was 99 F.; the pulse rate, 80 per minute, and respirations, 26 per minute. The blood pressure was 170 systolic and 100 diastolic. The patient was admitted to the Chester Hospital, where the diagnosis was confirmed bacteriologically (fig. 12). The patient was placed on sulfathiazole therapy—4 Gm. as an initial dose, followed by a dose of 1 Gm. every four hours. The urine contained a faint trace of albumin and an occasional hyaline cast. A blood count showed 4,550,000 red cells, a hemoglobin content of 13.5 Gm. per hundred cubic centimeters (84 per cent) and 6,600 white cells, of which 77 per cent were polymorphonuclear neutrophils, 2 per cent were eosinophils and 21 per cent were lymphocytes.

On March 3 the lesion showed little change, but the edema had spread across the back of the neck, which felt hard, and anteriorly along the entire cervical space. On March 4 there was noted a further spread of the soft swelling, with obliteration of the normal contour of the neck and face on the right side. The skin over the swollen area was bright red. A large lymph node was palpable above the right clavicle. There was a rise in temperature and increased toxicity. I decided to resort to serotherapy if improvement did not set in by the next morning. When seen at 7:30 a. m. the patient was drowsy and disoriented. The pulse was rapid, thready and irregular, due to extrasystoles. Cheyne-Stokes breathing and deep cyanosis had developed. The lesion had undergone marked changes. It covered a square 3 inches (7.5 cm.) wide and consisted of several large bluish red vesicles, from which a serosanguineous fluid oozed freely. The





center was black, but there was no definite eschar. The swelling had increased further, involving both sides of the neck (mumpslike appearance), the suprascapular area and the right infraclavicular fossa. The blood level of sulfathiazole was 8.3 mg. per hundred cubic centimeters. The last dose was given at 9 a. m. Chemotherapy was then stopped. A blood culture was sterile, and a blood count showed 3,910,000 red cells, a hemoglobin content of 11 Gm. per hundred cubic centimeters (68 per cent) and 14,900 white cells, of which 95 per cent were polymorphonuclear neutrophils (35 per cent segmented forms, 56 per cent band forms, 2 per cent metamyelocytes and 2 per cent myelocytes) and 5 per cent were lymphocytes. The urine contained albumin (4 plus), an occasional hyaline cast and numerous sulfathiazole crystals. One thousand cubic centimeters of lyophilized antianthrax serum (Sharp and Dohme) was given intravenously, followed by 500 cc. of physiologic solution of sodium chloride. This was followed by a severe chill that lasted one-half hour. Three hours later (4:30 p. m.) the patient was much improved. The pulse had regained its former full volume and was regular. Breathing was normal. The edema of the face was slightly decreased. At 9 p. m., the temperature was down to 90 F., and the patient felt much better. The swelling under the chin was softer, and the face was less swollen.

On March 6 the patient's general condition was good. The output of urine was excellent. The neck was definitely less swollen, although there was still considerable edema under the chin and along the right side of the jaw. An additional dose of 200 cc. of lyophilized antianthrax serum was given intravenously, without any reaction.

On March 7 the blood pressure was 160 systolic and 90 diastolic. The edema was decreasing rather slowly, and some dry black specks developed in the lesion, indicating eschar formation. On March 9 the edema of the neck had disappeared except for an area of induration around the large "pustule." The epiclavicular node was still palpable under the overlying swelling of the soft tissues. Sulfathiazole ointment was applied locally. On March 11 serum sickness became manifest. Urticaria, erythema, swelling of the hands, pruritus and fever lasted for the next five days. On March 16 the lesion had a dry black eschar the size of a 50 cent piece and was surrounded by an area of induration and bluish red discoloration of the skin. The lymph nodes were no longer palpable. The patient was sent home. The ulcer ran an indolent course. The eschar separated slowly and did not slough out until April 14. Anthrax bacilli were recovered from the lesion as late as April 6. Secondary pyogenic infection occurred, and the ulcer did not heal until May 9. The patient returned to work two days later.

Although 29 Gm. of sulfathiazole was ingested and retained in three days and a good blood level was secured, the patient failed to respond to it. Recovery ensued only after the intravenous injection of large doses (1,200 cc.) of antianthrax serum.

CASE 59.—T. W., a boy aged  $3\frac{1}{2}$ , was well until May 14, 1942, when his mother noticed a small "sore" on the inner surface of the left arm. On May 15 it became larger and red. Examination of the upper portion of the left arm revealed a superficial brownish ulceration of the skin the size of a dime. There was neither erythema nor edema. Four small lymph nodes were palpable in the left axilla. They were not tender. The temperature at 9 p. m. was 99.4 F. Next morning the lesion was typical of anthrax, and the diagnosis was confirmed bacteriologically. The parents lived in the village near the mill, and the boy played close to the

The child was admitted to the Chester Hospital on May 16 (weight, 30 lb. [14 Kg.]). He was given 1 Gm. of sulfathiazole, followed by 0.5 Gm. every four hours for four doses, then 0.25 Gm. every four hours.

[illegible]

morphonuclear neutrophils, 2 per cent were eosinophils, 4 per cent were monocytes and 14 per cent were lymphocytes.

One patient was seen in consultation with Dr. S. J. Diamond, of Woodlyn, Pa., and 2 patients were treated for the first few days by Dr. P. de Furia, of Chester.

314 East Broad Street.

# POLYMYOSITIS

## REPORT OF A FATAL CASE

DOUGLAS GOLDMAN, M.D.

CINCINNATI

Widespread inflammatory lesions of skeletal muscle are sufficiently rare to require special notice when they are encountered, particularly when the clinical aspect of the lesions has been entirely overlooked by a number of able clinicians. Inflammatory lesions of muscles are usually classified as (1) primary suppurative myositis, (2) dermatomyositis, (3) neuromyositis, (4) primary myositis fibrosa<sup>1</sup> and (5) progressive myositis ossificans. In addition, the "lymphorrhages" of myasthenia gravis can be considered a form of muscle inflammation. The literature on these conditions consists of relatively few reports of cases except for instances of dermatomyositis, and the cases are classified by descriptive criteria which seem in some instances to be vague and confusing. Dermatomyositis has been studied and an adequate review of the literature presented by Wolf and Wilens<sup>2</sup> and Wheeler and Harbin.<sup>3</sup>

## REPORT OF CASE

J. K., a Jewish optometrist aged 63 years, was first seen on Aug. 31, 1936. His original complaint was a cracking, vesiculated and and keratotic eruption on the hands and between the toes. This responded to application of a simple salicylic acid ointment. The patient was seen again December 25. He had noted that his hands and face had been puffy and swollen for about three or four weeks. He did not feel sick in any way, however. Physical examination at this time revealed early opacities of both lenses; heart size, rhythm and sounds within normal limits and blood pressure of 115 systolic and 75 diastolic. The previous cutaneous lesions were not noted, and the puffiness of which the patient complained was minimal.

Laboratory examination of the blood yielded the following data: red cell count, 4,850,000; white cell count, 9,600, with 68 per cent neutrophils, 28 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils; hemoglobin content, 14.8 Gm. per hundred cubic centimeters; 100 mg. of sugar and 32 mg. of nonprotein nitrogen per hundred cubic centimeters, and negative Wassermann and Kahn reactions. The urine had a specific gravity of 1.025; was acid, and clear; gave negative reactions for albumin, sugar and acetone and a negative reaction for

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1. Steiner, W. R.: Myositis, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, p. 353.

2. Wolf, A., and Wilens, S. L.: Dermatomyositis: A Report of Two Cases with Complete Autopsy, *Am. J. Path.* **12**:235, 1936.

3. Wheeler, P. H., and Harbin, M. W.: Dermatomyositis, *Arch. Dermat. & Syph.* **26**:1039 (Dec.) 1932.

indican, and was not abnormal on microscopic examination. The impression at this time was that the patient was worried about his condition, but no clearcut positive evidence of disease was obtained.

The patient was not seen again until June 9, 1937. He had consulted a competent dermatologist in March but had not followed the treatment recommended. The dermatologic diagnosis was fungous infection of the feet, with possible contact dermatitis. A patch test with oil of turpentine yielded a positive reaction. On June 9 the patient returned complaining of continued or recurring swelling and dermatitis of the hands and face. He stated that at times he had a generalized eruption with more itching than eruption. Physical examination at this time revealed nothing essentially abnormal except the cutaneous changes. His weight was 152 pounds (69 Kg.). The patient was placed on an elimination diet and given ephedrine by mouth, with apparent definite relief. On June 15 the patient first complained of his right leg being stiff and painful. This was (in retrospect) the first symptom of muscular involvement. On examination the extremity was

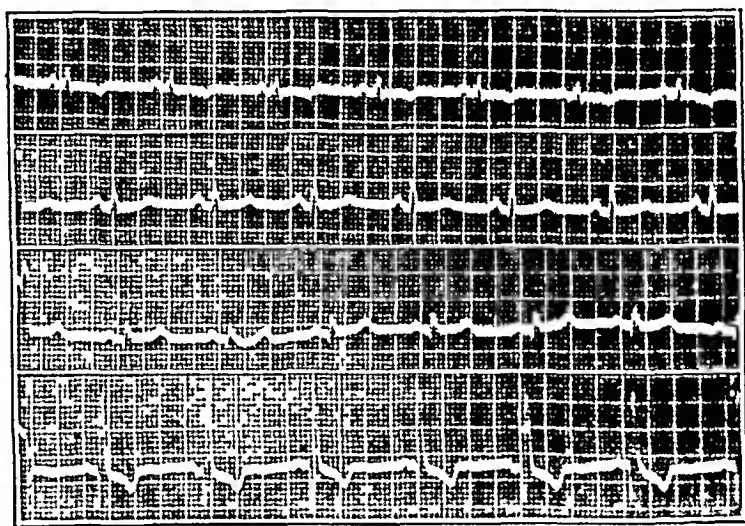


Fig. 1.—Electrocardiogram taken June 23, 1937. There is low voltage of the QRS complexes in all leads. The T wave in lead I is inverted, and the QRS complex in lead II is slightly slurred. The chest lead was made before the present standardization of chest leads was established, and the polarity is the reverse of the present lead IV F.

essentially normal. The patient was given intravenous injections of calcium gluconate twice weekly for three weeks, with no relief. Examination on June 23 showed swelling of fingers, a blood pressure of 103 systolic and 70 diastolic and a normal cardiac status. An electrocardiogram (fig. 1) showed low voltage in all leads and an inverted T wave in lead I. The blood contained 76 mg. of sugar per hundred cubic centimeters at 4 p. m. after a regular meal at noon. On June 27 the basal metabolic rate was  $-4$  per cent. One grain (0.06 Gm.) of thyroid was given daily for two weeks, chiefly because of the electrocardiographic changes in a nonobese person (5 feet 8 inches [173 cm.], 141 pounds [64 Kg.] at this time). No benefit accrued. Pains in the arms became troublesome in July, but physical therapy and drug treatment failed to bring relief. The patient disappeared from view until November 30. He consulted various physicians, and Drs. L. Schiff and C. D. Aring have provided an interim report. The results of

physical examination did not change until October, when the patient had sudden generalized muscular weakness, with acute difficulty in swallowing and phonation. Esophagoscopy examination failed to reveal any obstruction of the air or food passages. The impression from a neurologic examination (C. D. A.) was that the patient had an atypical form of bulbar palsy. It was particularly noted that the characteristic fibrillary tremors of bulbar palsy were absent. The patient became dissatisfied with the local medical talent, since he felt himself getting worse. He consulted physicians at the Mayo Clinic, who after thorough investigation concluded also that the patient had an atypical bulbar palsy, noting also the absence of fibrillary twitchings. On laboratory examination the urine, blood and cerebrospinal fluid were normal. When the patient was seen on November 30, after an interval of about four months, the change in his appearance was striking. Marked wasting of muscles was evident, and weakness of the pharyngeal muscles was apparent in the nasal quality of his speech and frequent nasal regurgitation after swallowing. Vibratory sense was diminished at both ankles, and the patient noted an intermittent, mild diarrhea and a sore tongue. In retrospect, these nutritional changes were probably secondary to inability to swallow. At the time the diagnosis of bulbar palsy seemed unacceptable, and severe polyneuritis and myasthenia were considered as therapeutic possibilities. Large doses (large for the time, 10 mg., the largest available ampule) of thiamine hydrochloride were given intravenously once or twice daily, and liver extract concentrates were administered at irregular intervals. Vibratory sense returned slightly on the right side, and swallowing improved somewhat, more from the patient's learning to "get around" the weakness than from improvement in the muscles. Prostigmine bromide in doses of 15 to 30 mg. three times a day was without effect over a period of five days. On Jan. 12, 1938 it was noted that the patient was having much more difficulty in speaking. Death occurred during the following night.

It was believed that an adequate clinical diagnosis had not been made, so permission for necropsy was obtained.

*Necropsy Report.*—The body was that of an extremely emaciated white man of late middle age. It was 162 cm. long.

The eyes, nose and mouth appeared normal. The tongue appeared fairly normal but somewhat atrophic. The structures of the neck showed marked atrophy of skeletal muscle. The sternocleidomastoid was pale, a mere slender cord, both on the right and the left side. The trapezius was likewise atrophic. The muscles of the trunk showed similar pallor and atrophic change and in addition had a gelatinous consistency and appearance. The spinal musculature, particularly the psoas, showed marked involvement in similar change. The skin appeared everywhere clear. Panniculus adiposus was practically absent throughout. The ribs and the costal cartilages appeared normal. The thoracic organs *in situ* did not show any change worthy of note. There was slight thickening in some areas of epicardium to form so-called "milk spots." Section of the lungs, both right and left, revealed no abnormality except slight congestion in both bases posteriorly. The bronchial tubes and the pulmonary vascular tree appeared normal.

The chambers of the heart had a normal appearance. There was slight sclerotic change evident in the mitral and the aortic valve leaflets, but quite insufficient to produce any functional change. The myocardium was slightly pale but not otherwise abnormal. The coronary vascular system showed a few sclerotic patches, but there was no tendency to ulceration or occlusion of the vessels.

The abdominal organs *in situ* appeared normal. The gastroenteric tract was traced from the pharynx to the anus. No abnormality was found. The liver was

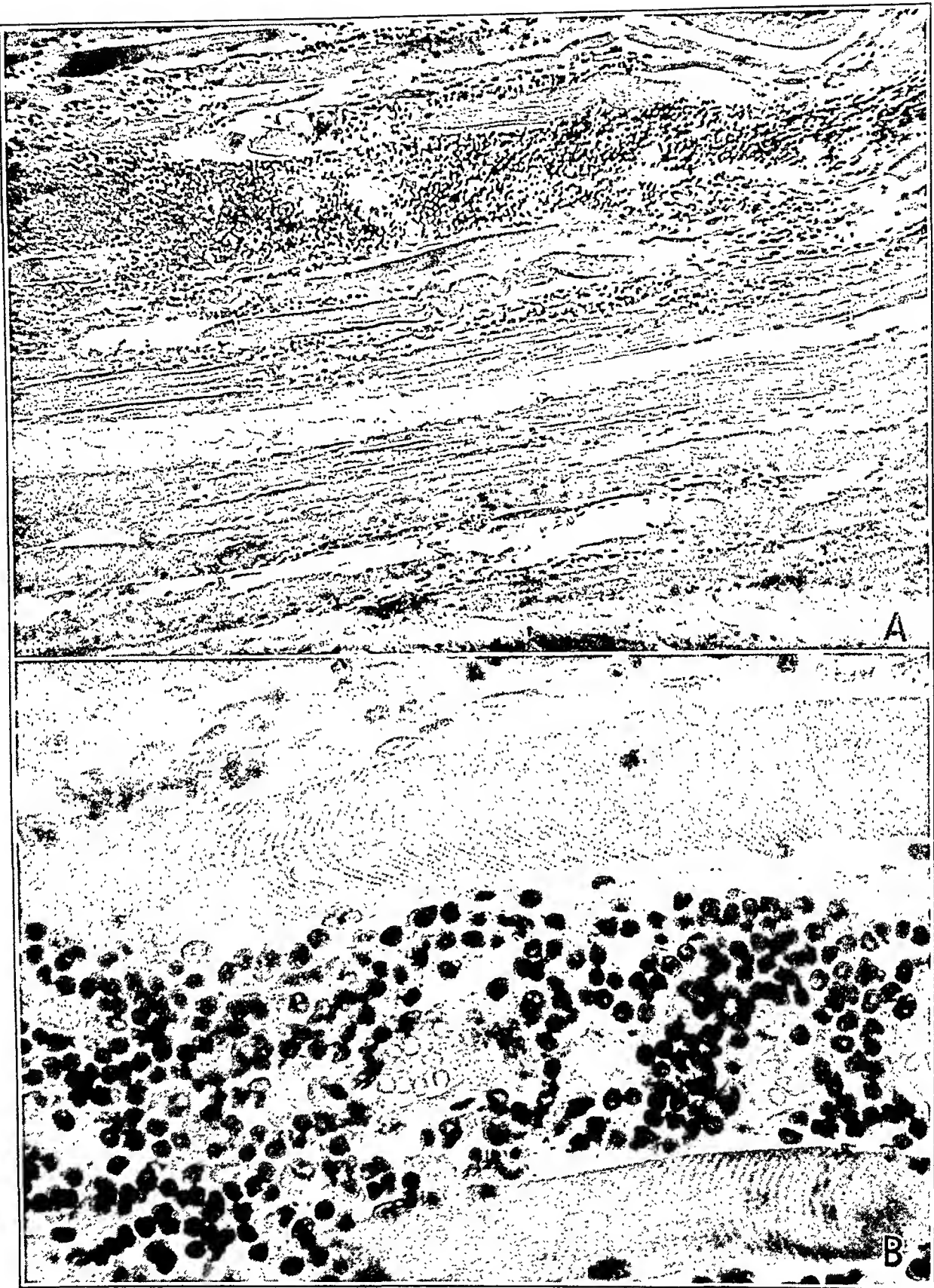


Fig. 2.—Sections from the psoas muscle, showing fragmentation of muscle fibers; hyalinization, and degeneration of fibers, with loss of striations, increase in muscle nuclei and marked infiltration with lymphocytes, monocytes and polymorphonuclear cells. A,  $\times 113$ . B,  $\times 450$ .

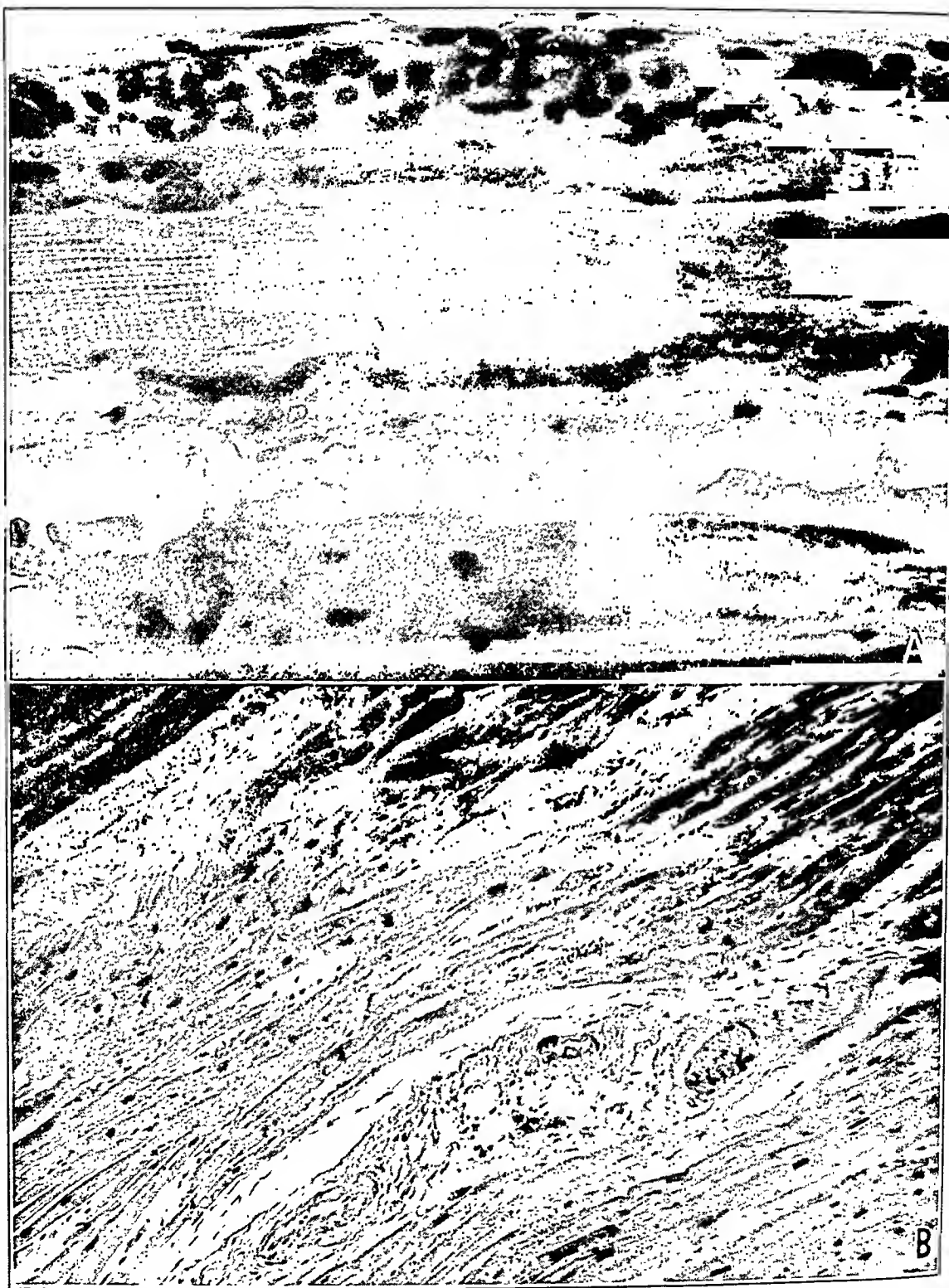


Fig. 3.—*A*, section from a sternomastoid muscle,  $\times 450$ . *B*, a section of heart muscle, showing arteriolosclerosis with secondary myocardial fibrosis.



of normal size. The contents and lining of the gallbladder appeared normal. On cut section the liver was not abnormal. The pancreas appeared relatively normal. The spleen was somewhat small and somewhat more fibrotic than average. The kidneys were of average size. The capsules stripped fairly readily but left a moderately finely lobulated surface. On cut section the kidneys were not grossly abnormal. The ureters and renal pelvises did not show any apparent change. The bladder and the prostate appeared normal.

The thyroid gland was apparently normal. The thymus was not found. No enlargement of the lymph nodes in any portion of the body could be determined.

The skull appeared normal. The component bones were somewhat softer than average. The brain showed normal configuration of both hemispheres. There was slight congestion evident over the cortex. A coronal section of the brain did not reveal any abnormality, and one section into the medulla at the level of the olivary nucleus failed to reveal gross damage. The membranes covering the brain appeared normal, and the mastoid cells when opened from the inside were not abnormal.

**Anatomic Diagnoses:** The anatomic diagnoses included gelatinous degeneration of skeletal muscle, probably representing generalized polymyositis; mild generalized arteriosclerosis, and extreme malnutrition.

**Microscopic Examination:** The most marked change evident was in the skeletal muscles. Muscle fibers from all regions of the body from which sections were obtained showed a marked hyaline degenerative process, with marked infiltration of lymphocytes, monocytes and polymorphonuclear cells (figs. 2 and 3).

In addition, there was generalized arteriolar thickening involving practically every organ (figs. 2 and 3). Pulmonary congestion was the only other evident change.

**Report of the Laboratory of Neuropathology (C. D. A.):** The neuropathologic diagnosis was "chronic cell change" in the medulla and the cerebral cortex. On the basis of clinical data this condition belongs under that broad heading of the bulbar palsies. A detailed description of neuropathologic observations may be the subject of a separate full report.

#### COMMENT

Of chief interest are the clinical course, the laboratory data and the necropsy report. No diagnosis worthy of the name was made during life, in spite of much consultation. Even when the muscles of respiration and deglutition were involved in the last stages of illness, diagnostic effort was directed to the nervous system rather than toward skeletal muscle. A long-drawn-out course with insidious onset, protean symptoms and generally equivocal and negative findings, should henceforth immediately direct attention to such diseases as periarteritis nodosa, dermatomyositis and fibrositis. One or more biopsies of skin and muscle should establish a diagnosis. In self-critical retrospect this was the chief omission in the management of the case. It is believed that the early cutaneous lesions should place this condition in the dermatomyositis group in spite of the relatively normal appearance of the skin in the late stages of the disease. Unfortunately, when the patient was first seen, the involvement of skeletal muscle was minimal, and later, when the myositis was devastatingly active, cutaneous manifestations were



minimal. Unfortunately also, the physicians who first saw the cutaneous manifestations did not again see the patient until the terminal stages of the disease, and those who saw the relatively acute early muscle symptoms hardly realized that any dermatologic manifestations had preceded them. It is only in retrospect that the clinical picture can be adequately synthesized. It is interesting to refer to a case of a somewhat similar condition reported by Hendry and Anderson,<sup>4</sup> in which cutaneous changes antedated involvement of muscle.

The outstanding pathologic feature of the case is the intensity and the extent of involvement of skeletal muscle (figs. 2 and 3). Special stains of material from the lesions failed to reveal any possible etiologic organisms. Special cultures were not made at the necropsy, since the microscopic observations were unexpected.

The neuropathologic changes are best interpreted as being secondary to the muscle degeneration—the reverse of a more common relation.

The neurologic clinical manifestations served only to confuse the issue and distort the interpretation of the changes in the skeletal muscles which were probably primary. The changes in the brain stem observed by Dr. Aring were to be expected with such extensive damage to the motor apparatus.

The absence of change in the heart muscle except from arteriosclerosis and arteriolosclerosis may be of differential importance. The intensity of the changes in the skeletal muscles calls for emphasis. Changes of this order had never been encountered previously by several experienced pathologists, who felt that myasthenia gravis and dermatomyositis usually showed much less devastating muscle change. The fact that widespread anatomic change was present with little or no abnormality in the results of routine laboratory examination again emphasizes the importance of clinical acumen and experience.

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4. Hendry, A. W., and Anderson, T. E.: Dermatomyositis, *Lancet* 1:80, 1939.

# SODIUM *d*-LACTATE TOLERANCE AS A TEST OF HEPATIC FUNCTION

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After studies on normal persons<sup>1</sup> and on patients with acute diffuse hepatic parenchymal injury<sup>2</sup> it was proposed that the utilization of intravenously injected sodium *d*-lactate be employed as a test of hepatic function.<sup>3</sup> The test was used in differential diagnosis of jaundice due to extrahepatic biliary obstruction and jaundice due to hepatic parenchymal damage. When compared to other tests of hepatic function the sodium *d*-lactate tolerance test proved to be most helpful in differentiating the two types of jaundice.<sup>3</sup>

The present paper deals with further studies on the use of intravenously injected sodium *d*-lactate as a differential diagnostic test between obstructive and nonobstructive jaundice.

As previously indicated,<sup>4</sup> the test is physiologically dependent on the ability of normally functioning hepatic cells to convert blood *d*-lactate into glycogen. The dextrorotatory form of lactic acid is the physiologically occurring isomer which is encountered as an intermediary in the carbohydrate cycle involving muscle and liver. Meyerhof and Lohmann<sup>5</sup> showed that isolated rat hepatic tissue was capable of synthesizing carbohydrate from dextrorotatory lactic acid but could do so to only a slight extent from levorotatory lactic acid. Cori and Cori,<sup>6</sup>

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1. Soffer, L. J.; Dantes, D. A.; Newburger, R., and Sobotka, H.: Metabolism of Sodium *d*-Lactate: I. Utilization of Intravenously Injected Sodium *d*-Lactate by Normal Persons, Arch. Int. Med. **60**:876 (Nov.) 1937.

2. Soffer, L. J.; Dantes, D. A.; Newburger, R., and Sobotka, H.: Metabolism of Sodium *d*-Lactate: II. Utilization of Intravenously Injected Sodium *d*-Lactate by Patients with Acute Diffuse Parenchymal Injury of the Liver, Arch. Int. Med. **60**:882 (Nov.) 1937.

3. Soffer, L. J.; Dantes, D. A., and Sobotka, H.: (a) Sodium *d*-Lactate Blood Clearance as a Test of Liver Function, Proc. Soc. Exper. Biol. & Med. **36**:692, 1937; (b) Utilization of Intravenously Injected Sodium *d*-Lactate as a Test of Hepatic Function, Arch. Int. Med. **62**:918 (Dec.) 1938.

4. Soffer, Dantes, Newburger and Sobotka (footnotes 1 and 2).

5. Meyerhof, O., and Lohmann, K.: Ueber den Unterschied von *d*- und *l*-Milchsaure für Atmung und Kohlehydratsynthese im Organismus, Biochem. Ztschr. **171**:421, 1926.

6. Cori, C. F., and Cori, G. T.: Glycogen Formation in the Liver from *d*- and *l*-Lactic Acid, J. Biol. Chem. **81**:389, 1929.

after injecting 95 mg. per hundred grams of body weight per hour of *d*-lactic acid into rats, demonstrated that there did not occur any appreciable increase in the lactic acid content of the blood or the urine. From 40 to 95 per cent of parenterally or orally administered *d*-lactic acid was found to be retained in the liver as glycogen; none was excreted in the urine. When these authors gave sodium *l*-lactate in the same dose, however, hardly any glycogen was formed in the liver and 30 per cent was excreted in the urine. Himwich, Koskoff and Nahum,<sup>7</sup> working on decerebrate dogs, found the muscles to be the main site of lactic acid formation. The liver was concerned with the removal of lactate from the blood and its probable conversion into glycogen. Cori and Cori<sup>8</sup> found that in normal rats injections of epinephrine caused a disappearance of muscle glycogen and formation of liver glycogen from the blood lactic acid.

#### METHOD

With a patient at rest in bed and having fasted for at least twelve hours, 75 mg. per kilogram of body weight of sodium *d*-lactate as a 12 to 14 per cent solution was injected intravenously. A control sample of blood was taken before the injection and another specimen thirty minutes after the injection.<sup>2</sup> The specimens were collected with sodium fluoride as the anticoagulant. Lactic acid determinations in duplicate were made by the method of Friedemann and his colleagues.<sup>9</sup> No untoward reactions were observed after the injection of sodium *d*-lactate.

#### RESULTS

The results obtained with the sodium *d*-lactate tolerance test on 63 patients with jaundice are presented. Some of these were previously reported.<sup>3</sup>

With the dose employed, normally functioning hepatic parenchymal cells are capable of removing all or almost all of the injected lactate within thirty minutes.<sup>3</sup> The retention of 5 mg. per hundred cubic centimeters or more of the injected lactate above the control level after a half hour is regarded as indicating hepatocellular injury.

In table 1 are recorded data on 36 patients with jaundice resulting from acute diffuse hepatic parenchymal injury. Thirty-four of the 36 patients retained 5 mg. per hundred cubic centimeters or more of the

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7. Himwich, H. E.; Koskoff, Y. D., and Nahum, L. H.: Changes in Lactic Acid and Glucose in the Blood on Passage Thru Organs, *Proc. Soc. Exper. Biol. & Med.* **25**:347, 1928.

8. Cori, C. F., and Cori, G. T.: Mechanism of Epinephrine Action: Influence of Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, *J. Biol. Chem.* **79**:309, 1928.

9. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: Determination of Acetic Acid, *J. Biol. Chem.* **73**:335, 1927. Friedemann, T. E., and Kendall, A. I.: Determination of Lactic Acid, *ibid.* **82**:23, 1929.

intravenously injected sodium *d*-lactate. The results obtained on 24 patients with extrahepatic biliary obstruction are presented in table 2. The diagnosis was confirmed either by operation or by postmortem examination in all instances. Only 4 of the 24 patients showed an

TABLE 1.—*Results of Hepatic Function Tests on Thirty-Six Patients with Jaundice Due to Diffuse Hepatic Parenchymal Injury*

Patient	Blood Lactic Acid Retention After 30 Min., Mg./100 Cc.	Ratio of Total to Esterified Cholesterol	Urinary Excretion of Hippuric Acid (Sodium Benzoate Test), Gm. in 1 Hr.	Urinary Excretion of Galactose, Gm. in 5 Hr.	Urinary Excretion of Urobilinogen	Diagnosis
1	10.8	300/115	0.66	4.33	...	Catarrhal jaundice
2	9.4	220/45	2.05	3.88	...	Catarrhal jaundice
3	9.9	325/87	0.95	1.85	...	Catarrhal jaundice
4	5.0	290/95	1.02	2.08	...	Catarrhal jaundice
5	9.6	260/120	1.18	1.50	...	Catarrhal jaundice
6	6.8	190/30	4.05	0.60	...	Catarrhal jaundice
7	26.1	180/55	0.53	5.50	...	Catarrhal jaundice
8	12.2	280/180	2.00	2.40	...	Catarrhal jaundice
9	6.3	210/35	0.96	5.40	...	Catarrhal jaundice
10	8.3	125/trace	0.99	5.50	...	Catarrhal jaundice
11	10.0	165/65	1.42	6.10	...	Catarrhal jaundice
12	17.6	210/35	3.10	2.73	...	Catarrhal jaundice
13	9.5	250/80	....	2.55	1:40	Catarrhal jaundice
14	7.2	.....	1.10	9.80	1:10	Catarrhal jaundice
15	4.3	470/230	0.76	0.93	1:160	Saline jaundice
16	10.4	575/270	2.30	....	1:10	Catarrhal jaundice
17	6.2	440/115	2.40	5.84	...	Catarrhal jaundice
18	10.8	260/55	....	....	1:160	Catarrhal jaundice
19	8.8	170/trace	0.26	5.00	1:20	Catarrhal jaundice
20	5.4	.....	....	....	...	Catarrhal jaundice
21	7.5	250/96	1.50	9.49	1:320	Arsphenamine jaundice
22	7.2	460/110	1.22	8.11	1:160	Arsphenamine jaundice
23	9.7	225/57	2.34	1.50	1:160	Arsphenamine jaundice
24	8.8	260/55	....	....	1:160	Arsphenamine jaundice
25	8.4	260/96	1.79	4.40	1:40	Arsphenamine jaundice
26	6.7	175/45	2.20	3.96	1:160	Arsphenamine jaundice
27	6.6	310/110	0.50	8.76	1:160	Arsphenamine jaundice
28	3.0	280/40	....	5.80	1:40	Catarrhal jaundice
29	8.0	170/70	....	2.02	1:610	Cirrhosis and catarrhal jaundice
30	7.5	250/110	....	8.50	1:80	Catarrhal jaundice
31	7.0	405/190	....	5.30	1:10	Catarrhal jaundice
32	6.8	595/290	....	5.30	1:4	Catarrhal jaundice
33	13.0	.....	....	8.30	1:10	Catarrhal jaundice
34	5.4	550/210	....	....	1:4	Catarrhal jaundice
35	20.0	490/145	....	1.30	1:160	Cirrhosis and catarrhal jaundice
36	10.6	240/65	....	10.1	1:4	Catarrhal jaundice

abnormal retention of sodium *d*-lactate. Three of these patients, however, were shown by biopsy at operation or by autopsy to have either severe cholangitis with associated hepatocellular damage (patients 5 and 20) or metastatic lesions and an abscess in the liver (patient 24).

A comparison of the results obtained with the sodium *d*-lactate tolerance test and other tests of hepatic function is shown in table 4. The ratio of total to esterified cholesterol, the utilization of orally

administered sodium benzoate, galactose tolerance and the urinary excretion of urobilinogen were determined simultaneously.<sup>10</sup> The sodium *d*-lactate tolerance test and the sodium benzoate test yielded positive results in the greatest number of patients with acute diffuse hepatic parenchymal injury. The ratio of total to esterified cholesterol indicated hepatocellular injury in two thirds of the patients, while the

TABLE 2.—*Results of Hepatic Function Tests on Twenty-Four Patients with Jaundice Due to Extrahepatic Biliary Obstruction*

Patient	Blood Lactic Acid Retention After 30 Min., Mg./100 Cc.	Ratio of Total to Esterified Cholesterol	Urinary Excretion of Hippuric Acid (Sodium Benzoate Test), Gm. in 4 Hr.	Urinary Excretion of Galactose, Gm. in 5 Hr.	Urinary Excretion of Urobilinogen	Diagnosis
1	...	830/470	3.37	3.60	...	Cancer of head of pancreas
2	...	425/150	0.80	....	...	Stone of common duct
3	...	415/220	1.50	1.08	...	Cancer of head of pancreas
4	...	430/110	3.15	....	1:5	Stone of common duct
5	9.7	225/57	2.35	1.50	1:160	Cancer of head of pancreas
6	4.0	270/78	....	0.90	...	Stone of common duct
7	4.8	385/170	0.82	1.80	1:40	Cancer of gallbladder and ducts
8	1.0	580/227	Positive	3.30	1:5	Cancer of head of pancreas
9	3.6	356/170	....	0.96	1:10	Stone of common duct
10	3.3	155/36	....	....	1:4; 1:640; 1:2	Stone of common duct
11	1.0	275/200	1.90	0.40	1:20	Stone of common duct
12	0.7	355/155	2.06	0.27	1:10	Cancer of gallbladder and ducts
13	1.4	440/250	3.79	0.69	1:80	Stone of common duct
14	1.0	430/115	....	2.10	1:10	Cancer of ampulla of Vater
15	...	285/160	2.00	2.10	...	Stone of common duct
16	1.2	520/355	1.50	....	1:10	Cancer of ampulla of Vater
17	4.8	215/130	....	3.90	1:80	Stone of common duct
18	...	345/125	....	1.00	1:2	Obstructive jaundice due to metastatic cancer of liver
19	3.0	.....	....	....	1:40	Stone of common duct
20	10.2	170/50	0.75	....	1:20	Stone of common duct with cholangitis and perforated gallbladder
21	...	345/125	....	1.00	1:2	Metastatic cancer of liver with obstruction
22	5.9	270/85	1.26	1.40	1:10	Cancer of head of pancreas
23	1.8	290/105	....	1.92	1:10	Cancer of head of pancreas
24	10.0	180/35	....	7.41	1:4	Cancer of head of pancreas with metastases and abscess in liver

galactose tolerance test yielded a positive result in a little over half of them. However, in the patients with extrahepatic biliary obstruction,

10. The following values for tests employed were accepted as evidence of hepatocellular injury: for the sodium benzoate test, a urinary excretion of less than 3 Gm. of hippuric acid during a four hour period; for the galactose tolerance test, a urinary excretion of 3 Gm. or more of galactose during a five hour period; for the urinary urobilinogen dilution test, a urinary excretion of urobilinogen in a dilution of 1:20 or higher, and for the ratio of total cholesterol to esterified cholesterol, a value of 40 per cent or less.

for 20 of 24 of whom the sodium *d*-lactate test yielded negative results, the sodium benzoate test gave a positive, and hence misleading, result in 11 of 14 instances in that it suggested diffuse hepatic injury.

The galactose tolerance test for 20 of 24 patients and the ratio of total cholesterol to cholesterol ester for 18 of 24 patients with extrahepatic biliary obstruction yielded results consistent with the diagnosis.

TABLE 3.—*Results of Hepatic Function Tests Suggestive of Obstructive Jaundice in Three Patients with Clinical Courses Suggestive of Hepatitis*

Patient	Lactic Acid Retention After 30 Min., Mg./100 Cc.	Ratio of Total Cholesterol to Cholesterol Ester	Excretion of Hippuric Acid (Sodium Benzoate Test), Gm. in 4 Hr.	Excretion of Galactose, Gm. in 5 Hr.	Excretion of Urobilinogen	Diagnosis
1	1.0	400/170	....	1.81	1:10	Hepatitis with intrahepatic biliary obstruction
2	2.0	300/170	....	2.84	....	Hepatitis with intrahepatic biliary obstruction
3	5.0	435/225	....	2.35	1:4	Hepatitis with intrahepatic biliary obstruction

TABLE 4.—*Comparison of Results Obtained with Hepatic Function Tests*

	Hepatitis			Extrahepatic Biliary Obstruction		
	Total No. of Patients	Result of Test		Total No. of Patients	Result of Test	
		Positive	Negative		Positive	Negative
Sodium <i>d</i> -lactate test.....	30	34	2	24	4	20
Ratio of total cholesterol ester.....	33	22	11	24	6	18
Galactose tolerance test.....	35	20	15	24	4	20
Sodium benzoate test.....	23	21	2	14	11	3
Urobilinogen test .....	22	15	7	21	8	13
		Total No. of Patients			Number of Patients for Whom Correct Diagnosis Indicated	
Sodium <i>d</i> -lactate test.....		60			54	
Ratio of total cholesterol to cholesterol ester.....		57			40	
Galactose tolerance test.....		59			40	
Sodium benzoate test.....		37			24	
Urobilinogen test .....		43			28	

It should be noted that of 3 patients with obstruction in whom the sodium *d*-lactate tolerance test indicated hepatocellular injury, subsequently proved by operation or necropsy, positive results were obtained on 2 with the sodium benzoate test, on 1 with the galactose tolerance test and on 3 with the ratio of total cholesterol to cholesterol ester.

Not included in table 4 are the results obtained on 3 patients under rather unusual circumstances. All hepatic function tests, including repetitions, on the patients yielded results consistent with a form of

obstructive jaundice. Their clinical course, however, suggested that of hepatitis. It is likely that all of these patients had intrahepatic biliary obstruction of the types described by Naunyn,<sup>11</sup> Siegmund<sup>12</sup> and Klemperer.<sup>13</sup>

#### COMMENT

An ideal hepatic function test should be capable of differentiating between jaundice due to diffuse hepatic parenchymal injury and jaundice due to extrahepatic biliary obstruction. The test would be intermediate in its sensitivity, i. e., able to indicate primary diffuse hepatocellular injury but insensitive to the secondary damage occurring with extrahepatic obstruction. Of the tests compared here, in my hands the sodium *d*-lactate tolerance test most closely approximates such a test. Because of the expense of the sodium *d*-lactate test it was deemed impractical to study its ability to indicate the progression or regression of hepatic parenchymal injury. In this respect, the remarks by Epstein and Greenspan<sup>14</sup> about the value of total cholesterol and cholesterol ester determination should be borne in mind. These authors stated that it is necessary to perform serial determinations of total and of esterified cholesterol in evaluating the state of hepatic function. They felt that a single determination might lead to erroneous conclusions. Our results tend to confirm their opinion. None of the tests employed was capable of indicating intrahepatic obstruction. The results obtained with the hepatic function tests on these patients were similar to those obtained on patients with extrahepatic biliary obstruction.

I have not employed the sodium *d*-lactate tolerance test for estimating hepatic function in the absence of jaundice, since satisfactory tests for this purpose already exist.

#### CONCLUSIONS

The results obtained with the utilization of intravenously injected sodium *d*-lactate as a test of hepatic function are described.

Thirty-four of 36 patients with jaundice due to diffuse hepatic parenchymal injury showed an abnormal retention of injected lactate.

In 4 of 24 patients with jaundice due to extrahepatic biliary obstruction there was an abnormal retention of injected lactate. Biopsy

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11. Naunyn, B.: Ueber Ikterus und seine Beziehungen zu den Cholangien, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:537, 1919.

12. Siegmund, H.: Selbständige intrahepatische Cholangitis, Beitr. z. path. Anat. u. z. allg. Path. **87**:425, 1931.

13. Klemperer, P.: Pathology of Icterus, New York State J. Med. **33**:1309, 1933.

14. Epstein, E. Z., and Greenspan, E.: Clinical Significance of the Cholesterol Partition of the Plasma in Hepatic and in Biliary Diseases, Arch. Int. Med. **58**: 860 (Nov.) 1936.

at operation or necropsy showed considerable associated injury to the hepatic cells in 3 of these 4 patients.

Comparative studies were made on the basis of the sodium benzoate test, the galactose tolerance test, the ratio of total to esterified cholesterol and the urinary urobilinogen dilution test.

In comparing the results obtained with the sodium *d*-lactate tolerance test and other tests of hepatic function, the lactate test yielded a greater incidence of correct results in the differential diagnosis of jaundice due to acute diffuse hepatic parenchymal injury and that due to extrahepatic biliary obstruction.

Drs. George Baehr and Eli Moschowitz permitted me to use the patients in their medical services as subjects in this study.

Chemistry Laboratory, Mount Sinai Hospital.



# Progress in Internal Medicine

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## SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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CHARLES F. MOHR, M.D.

AND

JOSEPH EARLE MOORE, M.D.

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The material for this article has been selected mainly from publications which have appeared from November 1941 to July 1942. As in previous reviews,<sup>1</sup> it has been necessary rigidly to select material. Because of the scarcity of journals from Europe there is a striking decrease in the number of foreign articles reviewed. The extensiveness of the literature on massive dose arsenotherapy necessitates its condensation into tabular form.

### HISTORY OF SYPHILIS

A brief history of syphilis is outlined by Kilduffe.<sup>2</sup> Arguments for and against the origin of the disease in the New World are discussed dispassionately, and its dissemination throughout Europe in the fifteenth century is described in graphic style. Interesting side lights and anecdotes make this article a readable summary, although the more recent control procedures designed to make syphilis "the next great plague to go" appear to have been slighted.

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins University and Hospital.

1. (a) Moore, J. E.: Syphilis: A Review of the Recent Literature, *Arch. Int. Med.* **56**:1015 (Nov.) 1935. (b) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **58**:901 (Nov.) 1936; (c) **60**:887 (Nov.) 1937. (d) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **62**:1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, *ibid.* **64**:1053 (Nov.) 1939. (f) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **66**:1112 (Nov.) 1940. (g) Mohr, C. F.; Padget, P.; Hahn, R., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **69**:470 (March) 1942.

2. Kilduffe, R. A.: The Next Great Plague to Go, *Mil. Surgeon* **90**:374 (April) 1942.

In his excellent biography of Columbus Morison<sup>3</sup> contributes the following note on the origin of syphilis:

No problem on Columbus's voyages has been so widely discussed as the question whether he did or did not import the syphilitic spirillum from America to Europe. Evidence that syphilis existed in a mild endemic form among the American Indians before 1492 is abundant. No certain evidence of syphilis in Europe exists before 1494, although certain medical historians assert the contrary. In any case, the disease appeared in a most virulent form in Italy in 1494, and spread rapidly. By 1520 it was generally believed in Europe that syphilis came from America, because a reputed cure for it, the guaiacum or *lignum vitae*, had been discovered there (doctrine of specifics). In view of the excellent health aboard homecoming *Niña* in 1493, and the absence of evidence to the contrary on *Pinta*, it seems highly improbable that Columbus's crews had then contracted the disease. But Las Casas states positively that the Indians gave it to the Spaniards, Oviedo definitely assigns the European importation to the Second Voyage, and Ruy Diaz de Isla, a Spanish physician whose book on syphilis appeared in 1539, assigns it to the First Voyage. He asserts that the disease was first observed at Barcelona in 1493, and that he treated some of the victims.

Two hypotheses are tenable. (1) Syphilis existed in both America and Europe in endemic form, and was stirred up by like events on both sides of the Atlantic, simultaneously: (a) the invasion of Italy by the French army under Charles VIII in 1494-1495, (b) the Spaniards roving and raping all over Hispaniola in 1494-1496. (2) The spirillum was brought to Europe in the blood stream of Columbus's captive Indians in 1493, and by them transmitted to public women in Barcelona, whence it crossed the Pyrenees and the Mediterranean.

The subject is discussed at length in the two-volume edition of this work, II 193-218.

The work of the pioneers in the study of cardiovascular syphilis is reviewed by Maynard.<sup>4</sup> Paré was the first to recognize that there was some connection between syphilis and aneurysm, although he believed treatment to be the cause. The first recorded statement that syphilis is the cause of aneurysm is attributed to Lancisii (1740). The first careful description of the pathologic anatomy of aortitis and aneurysm by Morgagni; the clinical observations of Corrigan on aortic regurgitation and of Ricord on syphilitic lesions of the myocardium; the description of syphilitic aortitis by Döhle, who recognized this to be the basic lesion on which aneurysm develops, and the demonstration by Reuter of *Spirochaeta pallida* in the aortic wall are all discussed directly from original source material.

Of interest is Gaumond's<sup>5</sup> history of syphilis among French-Canadians. Syphilis apparently reached Canada between 1776 and

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3. Morison, S. E.: *Admiral of the Ocean Sea: A Life of Christopher Columbus*, Boston, Little, Brown & Company, 1942, p. 359.

4. Maynard, E. P.: *Pioneers in Cardiovascular Syphilis*, J. Mt. Sinai Hosp. 8:841 (Jan.-Feb.) 1942.

5. Gaumond, É.: *La syphilis au Canada Français hier et aujourd'hui*, Laval méd. 7:25 (Jan.) 1942.

1780, where it was first designated "the disease of the Bay of Saint Paul," because of its frequency in that region; later it became known as *le mal de chicot*, *le mal des éboulements* and Ottawa disease. The first mention of the disease appears in the account of Cartier's second voyage. The bulk of evidence supports the view that syphilis did not exist, as an epidemic disease at least, among the Indians of Canada before the advent of the white man. Gaumond traces the evolution of syphilis in this area from the time of Cartier to the present day.

A readable account of the many superstitions connected with venereal diseases is given by Rolleston.<sup>6</sup> Weird and remarkable methods for the prophylaxis and the cure of syphilis are discussed and odd customs and traditions of primitive and exotic races are noted. Of special interest is the folklore concerned with the causation and the transfer of syphilis.

#### SPIROCHAETA PALLIDA

Using the electron microscope, Morton and Anderson<sup>7</sup> have studied unstained preparations of the Nichols strain of *S. pallida*. Thus tremendously magnified the organisms frequently were surrounded by a sheath, which occasionally formed thin tendrils projecting from the organisms. Granules, lateral buds and constrictions were observed.

Callaway and Sharp<sup>8</sup> have demonstrated that *S. pallida* will live for as long as twenty-seven hours in the developing chick embryo and that in some cases the organisms may retain their virulence for that length of time. It was not possible to determine whether there had been actual multiplication of the organism in this medium or whether the positive animal transfers represented merely survival of the initial inoculum.

In the cultivation and isolation of mouth spirochetes Wichelhausen<sup>9</sup> uses beef heart infusion broth containing cysteine hydrochloride and ascitic fluid. Purification of the cultures was done by centrifugation, filtration and growth on solid mediums anaerobically. Studies of the ability of various mouth spirochetes to attack carbohydrates and proteins were of no value, for none of the strains showed proteolytic or saccharolytic activity.

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6. Rolleston, J. D.: The Folk Lore of Venereal Disease, *Brit. J. Ven. Dis.* **18**:1 (Jan.-April) 1942.

7. Morton, H. E., and Anderson, T. F.: Observations on the Morphology of *Leptospira* and the Nichols' Strain of *Treponema Pallidum* with the Aid of the RCA Electron Microscope, *J. Bact.* **43**:64 (Jan.) 1942.

8. Callaway, J. L., and Sharp, J.: Cultivation of *Spirochaeta Pallida* on the Chorio-Allantoic Membrane of the Developing Hen Egg, *J. Lab. & Clin. Med.* **27**: 232 (Nov.) 1941.

9. Wichelhausen, R. H.: Cultivation and Isolation of Mouth Spirochetes, *J. Bact.* **43**:65 (Jan.) 1942.

Kolmer<sup>10</sup> indicates that fresh citrated human blood heavily seeded with virulent *S. pallida* may undergo spontaneous sterilization in about seventy-two hours when kept at 4 to 6 C.

*Accidental Inoculation.*—Shaw<sup>11</sup> summarizes the opinions of a group of outstanding syphilologists regarding the procedure to be followed in case of accidental inoculation with *S. pallida*. Approximately half of the group stated that local application of mild mercurous chloride ointment together with watchful waiting was the procedure of choice, whereas the other half recommended prophylactic injections of arsenicals and compounds containing heavy metals. In a collective experience of twenty-five such accidents syphilis did not develop in a single instance, regardless of whether local or parenteral therapy was used. Shaw himself recommends that injections of arsphenamine and a compound containing bismuth be withheld until a positive diagnosis can be established and that free bleeding and the local application of 33 per cent mild mercurous chloride ointment be employed at the time of the accident. The observation period, during which frequent serologic tests for syphilis are made, should be prolonged to at least ninety days.

#### EXPERIMENTAL SYPHILIS

*Immunity to Syphilitic Infection.*—Worms<sup>12</sup> reviews some of the factors affecting the development of immunity in experimental syphilis in rabbits, discussing (1) the interval between the first and the second inoculation, (2) the virulence and the size of the inoculum used in each inoculation, (3) the methods and the sites of the first and superinoculations and (4) the reaction of the rabbit to the first inoculation. Previously unpublished experiments lead Worms to conclude that under certain conditions there develops in untreated rabbits with latent syphilis a panimmunity to heterologous strains of spirochetes sufficient to suppress manifest lesions at the site of superinoculations.

Stratton<sup>13</sup> was interested in determining whether extracts prepared from apparently spirochete-free infectious animal tissues, unlike extracts prepared from tissues rich in organisms and unlike cultures grown on artificial mediums, would immunize rabbits to syphilitic infection or

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10. Kolmer, J. A.: A Note on the Survival of *Treponema Pallidum* in Preserved Citrated Human Blood and Plasma, *Am. J. Syph., Gonor. & Ven. Dis.* **26**:156 (March) 1942.

11. Shaw, C.: Accidental Inoculation with *Spirochaeta Pallida*, *Arch. Dermat. & Syph.* **44**:878 (Nov.) 1941.

12. Worms, W.: Some Factors Affecting the Development of Immunity in Experimental Syphilis, *Brit. J. Ven. Dis.* **18**:18 (Jan.-April) 1942.

13. Stratton, E. K.: The Effect of Immunization with Extracts of Syphilitic Tissue on the Course of Experimental Syphilis in Rabbits, *Am. J. Syph., Gonor. & Ven. Dis.* **26**:227 (March) 1942.

modify the course of the disease. Extracts were prepared from rabbit lymph nodes and from mouse brains. These extracts, rendered non-infectious by heat or a 40 per cent solution of formaldehyde, were injected both intracutaneously and subcutaneously into normal rabbits. Ninety days later the animals were inoculated with subscrotal grafts from fresh chancre tissue. None of the rabbits showed the slightest resistance to syphilis.

*Effect of Orchidectomy on Immunity to Syphilis.*—Hu and Tsao<sup>14</sup> have compared the course of experimental syphilis in 8 male rabbits bilaterally orchidectomized a year before inoculation with that in a group of 10 normal female animals. Inoculations were made intravenously, and the severity of the infection gaged by the following criteria: (1) the number of animals in which lesions developed; (2) the length of the incubation period; (3) the number, distribution and size of generalized lesions, and (4) the duration of activity of the disease. Their data indicate little significant difference between the two groups of rabbits. Since syphilis is normally more severe in the male animal, the authors conclude that the effect of orchidectomy is to increase the resistance of the male animal to syphilitic infection.

*Effect of Estrogens.*—The histologic changes in the testes of rabbits given prolonged treatment with estrogens and subsequently inoculated with *S. pallida* have been studied by Frazier and his co-workers.<sup>15</sup> Administration of estrogens and infection were both shown to depress the growth of the germinal epithelium. When the functional activity of the germinal cells had been depressed or completely arrested by estrogenic action, the testes became refractory to syphilitic infection and showed only slight alteration in histologic structure attributable to intratesticular inoculation with spirochetes or no change at all.

*Dispersion of S. Pallida in Mice.*—Having previously reported on the distribution of *S. pallida* in the white mouse (an animal in which experimental syphilis exists after subcutaneous inoculation as a symptomless infection), Levaditi and Rousset-Chabaud<sup>16</sup> studied the dispersion of the organism after intravenous and intracerebral inoculation. A considerable time discrepancy was noted between the infectiousness of lymph nodes (as judged by intratesticular inoculation of rabbits) and "dispersion" (dependent on finding the organism by microscopic study

14. Hu, C. K., and Tsao, S. N.: Increased Resistance to Syphilis in the Rabbit Following Bilateral Orchidectomy, Chinese M. J. **60**:118 (Aug.) 1941.

15. Frazier, C. N.; Hu, C. K., and Ma, W. C.: Relation of the Changes in Testicular Structure Induced in the Rabbit by Estrogenic Substance to Resistance Against Syphilis, Endocrinology **29**:218 (Aug.) 1941.

16. Levaditi, C., and Rousset-Chabaud, D.: Dispersion du "*Tréponema pallidum*" chez les souris blanches atteintes de syphilis inapparente, Bull. Acad. de méd., Paris **123**:984 (Dec. 17-24) 1940.

of tissue sections). The authors again suggest the existence of an invisible form of *S. pallida* to explain this discrepancy.

Levaditi and Rousset-Chabaud<sup>17</sup> also discuss the dispersion of *S. pallida* in the white mouse following inoculation into the peritoneum and on scarified skin, concluding that the organism disseminates less readily from these sites of inoculation than when injected intravenously, subcutaneously or intracerebrally.

*Oral Administration of Arsphenamine and Neoarsphenamine in the Treatment of Syphilis in Rabbits.*—Kolmer, Brown and Rule<sup>18</sup> report that both arsphenamine and neoarsphenamine administered orally are therapeutically effective in acute syphilitic orchitis of rabbits. Both drugs were rapidly absorbed from the gastrointestinal tracts of rabbits, as shown by high urinary excretion of arsenic. The single minimal curative dose of arsphenamine was 0.04 to 0.06 Gm. per kilogram by oral administration and that of neoarsphenamine about 0.08 Gm., these amounts being three to five times higher than the minimal curative doses by intravenous injection.

*Arsphenamine in the Treatment of Experimental Tuberculosis.*—Since the introduction of arsphenamine there has been controversy among clinicians and investigators as to its effect on tuberculous lesions occurring in syphilitic patients. McDermott, Webster and Macrae<sup>19</sup> have observed the effect of arsphenamine on tuberculosis in syphilitic animals. The rabbit was the animal of choice, since it was susceptible to both syphilis and tuberculosis.

Fifty rabbits which had previously had roentgen examinations of the chest and serologic blood tests for syphilis were inoculated intravenously with 0.5 cc. of a suspension containing 0.25 mg. of a bovine type of tubercle bacilli. Two weeks after injection all gave positive reactions to intracutaneous injection of old tuberculin.

Three weeks after inoculation with tubercle bacilli 32 of the animals were inoculated in the right testicle with 1 cc. of a testicular suspension of *S. pallida*. The animals were then divided into three groups, of which I and II comprised animals with both tuberculosis and syphilis and III those with tuberculosis alone. Animals in groups I and III were treated with 10 weekly injections of arsphenamine in doses of 10 mg. per kilogram of body weight. Those in group II were held as untreated controls.

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17. Levaditi, C., and Rousset-Chabaud, D.: La dispersion du "Tréponema pallidum" en fonction du mode d'inoculation, Bull. Acad. de méd., Paris **123**:762 (Nov. 5-26) 1940.

18. Kolmer, J. A.; Brown, H., and Rule, A. M.: The Oral Administration of Arsphenamine and Neoarsphenamine in the Treatment of Experimental Syphilis of Rabbits, Am. J. Syph., Gonorr. & Ven. Dis. **26**:63 (Jan.) 1942.

19. McDermott, W.; Webster, B., and Macrae, D.: The Effect of Arsphenamine on Tuberculosis in Syphilitic Animals, Am. Rev. Tuberc. **44**:604 (Nov.) 1941.

The clinical course of tuberculosis in these rabbits could be compared to that in other animals infected with the same strain of tubercle bacilli. Despite the moderately intensive arsphenamine therapy given to the animals in the present experiment, the course of tuberculosis was uninfluenced for the period during which the observations were maintained.

It is customary in this type of experimental tuberculosis for roentgenograms of the lungs to show considerable change in the first few weeks and eventually to show a remarkable degree of clearing. In the present series there was roentgen evidence of marked tuberculous involvement in the majority of animals before arsphenamine therapy. After ten weeks of such treatment, the rabbits were apparently healthy, the roentgen shadows had cleared almost entirely and the amount of tuberculosis demonstrated at autopsy was much less than that seen by roentgen examination before therapy. It is therefore believed that arsenical therapy did not prevent the healing of a large amount of the tuberculosis, and all animals had tuberculosis in the latent stage when the experiment was terminated.

There was no measurable difference in the amount of tuberculosis present in the two arsphenamine-treated groups, in one of which syphilis was coexistent. The control group of animals infected with both syphilis and tuberculosis, which received no arsphenamine, showed slightly but definitely more severe tuberculosis at autopsy.

The authors believe that although the groups are small, the percentage of variation is statistically significant and would indicate that tuberculosis coexisting with syphilis runs a less benign course when syphilis is not treated with arsphenamine.

*Infectiousness of Rabbit Semen.*—Whether untreated males with late syphilis may harbor spirochetes in their semen, and therefore be carriers of syphilis, has been studied experimentally by Kemp.<sup>20</sup> Adult male rabbits were inoculated in granulating wounds on the back, and infection was proved by the demonstration of *S. pallida* by dark field examination of serum expressed from the lesions which developed. Animals in which bilateral metastatic orchitis with atrophy of the testes developed were excluded from the subsequent experiment. Ninety-one to two hundred days after inoculation, after all open lesions were healed, each of 12 rabbits was caged with a normal female rabbit for thirty-nine to seventy days. The pairs were carefully observed, and unless coitus occurred at least four times, both male and female animals were discarded. The group of females was examined for evidences of syphilitic infection, and from one hundred and twenty to one hundred and thirty-five days after they were removed from the cages of the male rabbits, their popliteal

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20. Kemp, J. E.: The Infectiousness of the Semen of Rabbits with Late Syphilis, *Am. J. Syph., Gonor. & Ven. Dis.* **26**:16 (Jan.) 1942.

lymph nodes were removed, macerated in physiologic solution of sodium chloride and inoculated intratesticularly into 2 normal male rabbits. The transfer animals were observed ninety days for the development of orchitis.

No visible evidence of infection developed in any of the females, and their popliteal lymph nodes were noninfectious for normal male rabbits.

A second group of 12 female rabbits comprised the control group. Each animal was inoculated intravaginally with testicular suspensions containing *S. pallida*. They were examined for the development of genital lesions, and ninety days after inoculation the popliteal lymph nodes of the 10 in which there were no genital lesions containing spirochetes detectable by dark field examination were removed, emulsified and inoculated into 2 normal rabbits. Of the 12 females inoculated intravaginally, in 2 vaginal lesions developed in material from which spirochetes were demonstrable by dark field examination and in 8 an asymptomatic infection developed. Kemp's experiments suggest that

. . . the semen of rabbits with late syphilis is either free from treponemes or contains them in such few numbers that it is not infectious for female rabbits. In this regard the course of syphilis in rabbits apparently parallels fairly closely its course in man.

#### PINTA AND BEJEL

*Pinta*.—Pinta, mal del pinto and carate are one and the same disease, the etiologic agent being a spirochete indistinguishable morphologically from that of syphilis and of yaws. The recent advances leading to the modern concept of pinta are summarized by Pardo-Castello and Ferrer.<sup>21</sup>

Pinta resembles syphilis and yaws in its general evolution. It begins with an initial lesion, followed by disseminate macules and plaques. Precipitation and complement fixation reactions for syphilis are positive in 60 per cent of the cases of pinta in the early stages, and in 100 per cent in the late stages. In the series of patients studied by these authors, 52.1 per cent showed changes in the spinal fluid similar to those occurring in syphilis of the central nervous system and 64.5 per cent had cardiovascular changes, usually aortitis. Pardo-Castello believes that the mode of transmission of pinta is probably personal contact. It has been transmitted experimentally to human beings. The disease confers an immunity, but patients with active syphilis may acquire this infection.

*Bejel*.—Bejel is a spirochetel disease endemic among the nomadic inhabitants of the Euphrates River valley. Its clinical description has initiated a reconsideration of certain differences between syphilis and yaws and has led to a consideration of the relation of bejel to these diseases.

21. Pardo-Castello, V., and Ferrer, I.: Pinta; Mal del Pinto; Carate, Arch. Dermat. & Syph. 45:843 (May) 1942.



A different approach to the subject is provided by Rost,<sup>22</sup> who describes the diagnostic features of bejel demonstrable by roentgen examination. The osseous changes consist essentially of periosteal and endosteal proliferation, with varying degrees of rarefaction resembling at times the gummas of late syphilis. No osteochondrotic changes similar to those encountered in congenital syphilis were noted, and there were no neuropathic lesions of joints. The lesions of bones respond readily to small amounts of antisypilitic treatment.

#### SERODIAGNOSIS OF SYPHILIS

*Serologic Surveys.*—There is an increasing appreciation of the need for a system for gaging the efficiency of performance of the laboratory tests on which the physician places major reliance in the diagnosis of syphilis. For the past six years the Committee on Evaluation of Serodiagnostic Tests for Syphilis has been concerned with this problem and has published reports dealing with the standards of performance of tests in state laboratories.

The results of the 1941 survey are detailed in the most recent report.<sup>23</sup> For the first time the identity of the participating laboratories is revealed. There has been a sustained trend toward a more efficient performance of test methods and a more uniform standard of results in the large majority of state laboratories.

A preliminary report<sup>24</sup> of the Serology Conference held in Washington, D. C., in October 1941 is also available. The aim of the conference was to accumulate information as to the reliability of a group of relatively new technical methods for the serodiagnosis of syphilis. A total of 19 author-serologists or their representatives participated and carried out thirty separate procedures. Tabular and graphic summaries of the results with these thirty procedures on 1,002 specimens of blood and 234 specimens of spinal fluid are presented.

*Antigen.*—An extensive review by Weil<sup>25</sup> concerning the Wassermann antigen and related alcohol-soluble antigens covers two hundred and twenty-five references to the medical literature for the period from

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22. Rost, G. S.: Roentgen Manifestations of Bejel ("Endemic Syphilis") as Observed in the Euphrates River Valley, *Radiology* **38**:320 (March) 1942.

23. Parran, T.; Hazen, H. H.; Mahoney, J. F.; Sanford, A. H.; Sencar, F. E.; Simpson, W. M., and Vonderlehr, R. A.: Serodiagnostic Tests for Syphilis in State Laboratories: The 1941 Evaluation of Their Performance, *J. A. M. A.* **117**: 1167 (Oct. 4) 1941.

24. Parran, T.; Hazen, H. H.; Mahoney, J. F.; Sanford, A. H.; Sencar, F. E.; Simpson, W. M., and Vonderlehr, R. A.: Preliminary Report on the Washington Serology Conference, *Ven. Dis. Inform.* **23**:161 (May) 1942.

25. Weil, A. J.: The Wassermann Antigen and Related "Alcohol-Soluble" Antigens, *Bact. Rev.* **5**:293 (Dec.) 1941.

1925 to September 1941. No original work is reported, but the author adequately accomplishes his mission of integrating a complex subject to provide a basis for future investigation.

*Spirochetal Antigens in Serologic Tests for Syphilis.*—There is a large literature pertaining to the sensitivity, specificity and practical value of tests employing spirochetal antigens in the serologic diagnosis of syphilis. In view of the conflicting claims Kolmer<sup>26</sup> reviews the present status of such tests. He attempts to clarify the question as to whether, as suggested by Gaetgens and Beck, there occurs in syphilitic serum a specific antibody for *S. pallida* separate and apart from the reagin reacting with alcoholic extracts of beef heart or whether the Wassermann and the flocculation reaction, on the one hand, and complement fixation with spirochetal antigens, on the other, are due to spirochetal antibodies, as claimed by Eagle and Hogan.

The paper can best be summarized by quoting the author's summary and conclusions:

Complement fixation tests conducted with antigens of cultivated *S. pallida*, especially of the Reiter and Kazan strains, compare favorably in sensitivity with the Wassermann and flocculation tests in the serologic diagnosis of syphilis of human beings and rabbits, but their practical value . . . has not been sufficiently defined. [They] . . . are not as specific as the Wassermann and flocculation tests, largely because of the presence in normal serum of natural spirochetal antibody.

This natural antibody as well as that produced in syphilis is of a group character reacting not only with cultivated *S. pallida* but with *S. macrodentium*, *S. microdentium* and other spirochetes. . . .

Largely on the basis of absorption of syphilitic human serum with tissue lipids and suspensions of cultivated *S. pallida*, the preponderance of evidence is in favor of regarding the Wassermann reagin and spirochetal antibody as separate entities which may coexist in serum. . . .

The practical value of antigens of cultivated *S. pallida* in the serologic diagnosis of syphilis and in relation to the treatment of the disease can not be stated at present, but they are worthy of further study. If such strains are employed, antigens of whole spirochetes in phenolized saline solution appear to be advisable. The Reiter or Kazan strains are preferred, and a mixture of the two may be advisable. . . . Suspensions of virulent tissue spirochetes are preferred, but owing to technical difficulties in their preparation they probably cannot be employed.

Continuing their studies on the role of *S. pallida* in the Wassermann reaction, Kolmer, Kast and Lynch<sup>27</sup> describe a technic for obtaining an

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26. Kolmer, J. A.: Serologic Diagnosis of Syphilis: Value of Complement Fixation and Agglutination with Spirochetal Antigens and Relation of Spirochetal Antibody to the Wassermann Reagin, *Arch. Dermat. & Syph.* **45**:455 (March) 1942.

27. Kolmer, J. A.; Kast, C. C., and Lynch, E. R.: Studies on the Role of *Spirochaeta Pallida* in the Wassermann Reaction: III. Complement Fixation and Agglutination in Syphilis with Antigens of Tissue *Spirochaeta Pallida*, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:142 (March) 1942.

antigen suspension of virulent *S. pallida* (from acute testicular syphilomas of rabbits) relatively free from tissue debris and serum. This antigen was used to study normal and syphilitic human and rabbit serums for the presence of complement-fixing and agglutinating antibodies.

Fewer nonsyphilitic human and rabbit serums showed complement fixation or agglutination with suspensions of virulent tissue spirochetes than with cultivated spirochetes. In syphilitic human and rabbit serums spirochetal antibody was more active with tissue spirochetes than with nonvirulent cultured organisms. The authors believe:

This indicates that the *natural* spirochetal antibody is more active for non-virulent cultivated *S. pallida* than for virulent tissue spirochetes but that the acquired antibody is more active for the latter, suggesting that cultivated *S. pallida* may undergo dissociation with a change in antigenic structure associated with loss of virulence.

*Nature of Reagin.*—Ratcliffe<sup>28</sup> reviews the literature and briefly discusses the nature of syphilitic reagin, particularly in respect to whether this substance is an antibody to *S. pallidum* or to lipid haptens of the host, liberated at foci of infection and activated by spirochetal protein.

The author cites already reported substances which when injected into rabbits produce positive serologic reactions for syphilis and likewise reports the unsuccessful attempts of other investigators to produce artificially positive reactions in the serum of these animals. He points out that because of the incidence of spontaneously positive reactions in rabbits it is often difficult to interpret the significance of the serum change after the injection into the animal of some foreign substance. The consensus, however, is that it is possible artificially to induce a positive serologic reaction in the rabbit by methods which involve neither *S. pallida* nor any specific derivative of it.

In attempting to demonstrate evidence to support or controvert the autoantibody theory in accounting for nonspecific reactions obtained with lipoid antigens in a serodiagnostic test for syphilis, Ratcliffe subjected rabbits to various treatments intended to stimulate or to augment the production of reagin by nonspecific and noninfectious means. Two methods of study were employed: (a) producing pathologic lesions characterized by chronic inflammation and degenerative changes simulating the essential lesions of syphilis or (b) stimulating or augmenting the production of reagin by the injection of various extracts of homologous tissue or preparations of autogenous serum.

Among the procedures attempted were the injection of flocculate from human serum giving a positive reaction for syphilis, the intra-abdominal transplant of rabbit's aorta, ligation of the splenic pedicle and the injec-

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28. Ratcliffe, A. W.: The Role of Autoantibodies in the Serodiagnosis of Syphilis, *J. Lab. & Clin. Med.* **27**:729 (March) 1942.

tion of homologous tissue preparations. After each of these procedures some rabbits showed a definite increase in reagin titer. However, in many animals the change was either absent or minor. The author says:

While the evidence brought forward [by this work] is not entirely convincing, it is compatible with, and is best explained by, the conception that reagin is a closely related group of antibodies and not a single chemically constant compound, and that, while the primary serologic change in syphilis may be the formation of antibodies to *T. pallidum*, the potential or actual occurrence of positive or doubtful reactions with lipid antigens in the absence of syphilis results from the formation of antibodies to the "ubiquitous lipid," either from some other infectious agent or from the tissues of the host, dependent upon the liberation of lipid haptens and protein derivatives capable of activating them.

*Titration of Traces of Reagin.*—A technic used in the detection of isoagglutination in dried blood stains has been adapted by Lund<sup>29</sup> to the titration of traces of reagin. The basis of this procedure is the division of the flocculation test into two steps: (a) sensitization of the antigen, in which maximal volumes of serum and minimal quantities of antigen are used, and (b) secondary induction of flocculation by concentrating the sensitized antigen by centrifugation. By this method, proportions of serum in excess of those previously studied can be utilized, sensitivity can be increased and the definite quantitative relations which obtain permit reasonably accurate titrations.

Lund was able to demonstrate (1) that the sensitivity of a serologic test is dependent on the quantity of serum available for each unit of antigen and (2) that repeated doses of serum eventually bring about aggregation even if the individual doses are of "subtiter" value, thereby making possible the sensitization of antigen by amounts of serum which, if used in a single volume, would be too unwieldy for centrifugation.

A preliminary practical trial of the method was undertaken to determine whether reagin can be detected in normal serum and in the serum of patients with syphilis, both untreated and treated to become apparently seronegative, and also to see whether quantitative titrations of large proportions of serum have a reasonable degree of correlation with standard technics and the clinical aspects of the cases. The results suggest that standard flocculation tests can be made more sensitive by increasing the volume of serum in relation to the amount of antigen used and recovering the antigen by centrifugation, also that the use of unlimited volumes of serum in flocculation tests has no diagnostic value unless quantitative determinations are made. Lund concludes:

1. A practically unlimited increase of sensitivity can be obtained by treating each of the two stages of serologic aggregation as individual reactions. This is

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29. Lund, H.: The Titration of Traces of Reagin: Technique of Flocculation Using Maximal Serum Proportions with Secondary Recovery of Antigen, *Am. J. Syph., Gonorr. & Ven Dis.* **26:1** (Jan.) 1942.

done by adjusting the proportions to favor sensitization (a maximal dose of serum and a minimal dose of antigen) and secondarily modifying the conditions (by centrifugation and reconcentration of antigen) in order to induce aggregation. Experimentally, the sensitivity of a standard flocculation test for syphilis was increased 32 to 64 times.

2. By means of this procedure sensitivity depends upon the amount of serum available for each unit of antigen and is not limited to an optimal zone of dilutions.

3. Within a wide range, sensitivity is directly proportional to the amount of serum used and inversely proportional to the amount of antigen used in the reacting system. Increasing the volume of the reacting system by the addition of saline solution does not materially affect this rule. From this relationship, a convenient method of expressing titrations is evolved. This is to state the volume of undiluted serum required to aggregate an arbitrary unit of antigen.

4. The above experimental findings and the results of a preliminary clinical trial point to the possibility of placing the serology of syphilis upon a quantitative scale that far exceeds the scope of standard tests.

#### *Effect of Treatment on the Results of Quantitative Serologic Tests.*

—The effect on the Wassermann reaction of a single course of treatment with arsphenamine and a mercurial alone or in combination was observed in 145 patients by Belding.<sup>30</sup> Quantitative estimations of serum reagin were made before halfway through and one week after treatment and at subsequent intervals of four weeks for twenty-four weeks. Most of the patients observed had received previous treatment and were known to have late syphilis. The mean percentile reduction in reagin titer twenty-four weeks after one course of treatment was arsphenamine, 35; a mercurial, 29, and combined arsphenamine and a mercurial, 47. Previous treatment, the initial reagin titer, the duration of the disease and the total amount of treatment given all were found to influence the serologic response.

*Storage of Serums.*—Myers and Perry<sup>31</sup> report the comparative results of serologic tests for syphilis made on portions of the same serum specimens tested when fresh and after storage for one or two months at 2 to 4 C. and at —27 C. Their results indicate that storage of serum is not detrimental and that there is little choice between 2 to 4 C. and —27 C.

*Biologic False Positive Serologic Reactions for Syphilis.*—Mohr, Moore and Eagle<sup>32</sup> have reviewed the literature on the presence of reagin-like substance in the serum of normal human beings. They report

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30. Belding, D. L.: The Effect of Arsphenamine and Mercury upon the Wassermann Reaction, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:759 (Nov.) 1941.

31. Myers, R. M., and Perry, C. A.: The Storage of Syphilitic Serums, *Ven. Dis. Inform.* **23**:56 (Feb.) 1942.

32. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: I. Occurrence in Normal Persons, *Arch. Int. Med.* **68**:898 (Nov.) 1941.

9 instances of what they regard as biologic false positive reaction to serologic tests for syphilis in a normal nonsyphilitic person. The authors say:

The demonstration by three different groups of workers (Malloy and Kahn; Barnett, Jones and Kulchar; Sherwood, Bond and Canuteson) that some normal human serums may contain reagin or reagin-like factors is of obvious significance for the practical serologic diagnosis of syphilis. It is true that the amounts of reactive material which these workers have been able to demonstrate is well below the threshold concentration which can be detected by the standard diagnostic procedures. Under ordinary circumstances the reactivity of normal serum therefore does not complicate the diagnostic test. The 9 cases here presented, nevertheless, indicate that in the exceptional case this normal factor may be present in sufficient concentration to give biologic false reactions.

Despite these false reactions, it may be that the antibody present in syphilitic serum is strictly specific and that normal serum contains other substances with qualitatively similar effects on the lipoidal suspensions used as "antigen." Thus, a normal serum may be capable of causing the aggregation of these lipoidal suspensions to give clumps indistinguishable from those caused by syphilitic serum, despite the fact that the mechanism of the aggregation may be altogether dissimilar.

In a second communication Mohr, Moore and Eagle<sup>33</sup> call attention to the fact that many infectious diseases have been reported to cause biologic false positive serologic reactions for syphilis. In only a few of these (malaria, leprosy and infectious mononucleosis) can one arrive at some idea as to the incidence of these false positive reactions, whereas in such diseases as relapsing fever, rat bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infections, malignant conditions (particularly cancer of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphogranuloma venereum, trypanosomiasis, typhus fever, vaccinia and infections of the upper respiratory tract serologic tests for syphilis have been done neither on a large enough group of subjects nor frequently enough to establish definitely the incidence of false positive reactions.

There are reported here brief summaries of the records of 11 non-syphilitic patients with various diseases, in whom transitory biologic false positive serologic reactions for syphilis were observed. The conditions reported are a subacute infection of unknown cause, acute labyrinthitis of unknown cause, vaccinia, pneumonia, sore throat of unknown cause, infectious mononucleosis and rat bite fever.

The literature pertaining to biologic false positive serologic reactions for syphilis associated with the aforementioned conditions has been reviewed. The authors' justification for the publication of such a heterogeneous series of case reports as this lies in the fact that

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33. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: II. Occurrence with Organic Diseases Other Than Syphilis, *Arch. Int. Med.* **68**:1161 (Dec.) 1941.

attention is at once directed to the nonspecificity of serologic tests for syphilis and to the caution necessary in the interpretation of results. They point out that the nonspecificity extends to nearly all of the generally used technics for serologic tests for syphilis.

The occurrence of biologic false positive serologic reactions for syphilis in children is discussed by Bridgeman and Jacobson,<sup>34</sup> who report 18 cases. In addition to the conditions known to give false positive reactions in adults, children may have nonspecific reactions associated with an acute infectious disease with fever.

*False Positive Serologic Reactions Associated with Malaria.*—A study of the effect of malaria on serologic tests for syphilis in Negro patients from North Carolina is reported by Fellows.<sup>35</sup> In his series of 3,244 patients an incidence of 9.9 per cent positive serologic reactions for syphilis and of 3.1 per cent demonstrable malaria protozoa was encountered. When malaria parasites were found, disagreement between the first and the second serologic tests occurred in 64.8 per cent of the patients in whom the first test showed a positive or a doubtful reaction. Disagreement in patients for whom no parasites could be demonstrated was 24.8 per cent.

In a series of 11 nonsyphilitic patients with dementia praecox inoculated with malaria, Burney, Mays and Iskrant<sup>36</sup> found that all gave false positive serologic reactions for syphilis at some time by at least two different technics. The greatest number of positive reactions occurred fifteen to twenty-one days after the onset of clinical activity. Seldom did the positivity of any reaction extend over a period longer than four weeks. The duration of clinical activity, the highest temperature reached, the time of withdrawal of blood in relation to an individual paroxysm or the density of parasites did not notably influence the serologic reactivity. In stressing the public health significance of their results, the authors conclude that a diagnosis of syphilis based on serologic tests alone should not be made in an area where malaria is endemic without first eliminating the possibility of coincident malarial infection.

Unfortunately, there is not as yet any satisfactory information concerning the incidence of biologic false positive reactions in patients with chronic, as opposed to acute, malaria.

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34. Bridgeman, M. L., and Jacobson, L. D.: False Positive Serologic Tests for Syphilis in Children, *Northwest Med.* **40**:325 (Sept.) 1941.

35. Fellows, F. S.: Relationship of Malaria to Serologic Tests for Syphilis, *North Carolina M. J.* **2**:601 (Nov.) 1941.

36. Burney, L. E.; Mays, J. R. S., and Iskrant, A. P.: Results of Serologic Tests for Syphilis in Non-Syphilitic Persons Inoculated with Malaria, *Am. J. Pub. Health* **32**:39 (Jan.) 1942.

*False Positive Serologic Reactions Associated with Infectious Mononucleosis.*—The reason for transiently positive complement fixation and flocculation reactions for syphilis in patients with infectious mononucleosis is not known. Kolmer, Ginsburg and Lynch<sup>37</sup> suggest that the phenomenon may be due to the production of a lipoidophilic reagin by the infectious agent of the disease, rather than to a reaction between heterophile antibody in the serum and heterophile antigen in alcoholic tissue extracts.

*False Positive Serologic Reactions Associated with Lymphogranuloma Venereum.*—Chana<sup>38</sup> reports false positive serologic reactions for syphilis in 20 per cent of 122 cases of lymphogranuloma venereum. To determine whether concomitant syphilitic infection is present, the author believes the "verification test" of Kahn to be of value, since he found a close correlation between the results of this test and the ultimate serologic outcome.

*False Positive Serologic Reactions Associated with Rat Bite Fever.*—In a comprehensive article on the two types of rat bite fever, due, respectively, to *Spirillum minus* and to *Streptobacillus moniliformis*, Brown and Nunemaker<sup>39</sup> comment on the incidence of biologic false positive serologic reactions for syphilis occurring in the course of this disease. In the spirillary form it is well established that such false positive reactions occur in 50 to 60 per cent of reported cases. In the form due to *S. moniliformis* the number of reported cases is as yet small, but the incidence of false positive serologic reactions appears somewhat lower (about 37 per cent).

*Tests Purported to "Verify" the Results of Standard Serodiagnostic Tests.*—In 1940 Kahn<sup>40</sup> described a differential temperature procedure which, it was claimed, allowed separations of true from false positive serologic reactions. Chargin and Rein<sup>41</sup> have used the Kahn verification test in the study of 1,565 patients with various conditions, including syphilis, nonsyphilitic dermatoses, pregnancy, acute exan-

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37. Kolmer, J. A.; Ginsburg, I. W., and Lynch, E. R.: The Wassermann Reaction in Infectious Mononucleosis with Special Reference to the Kolmer Test, *Am. J. Clin. Path.* **12**:316 (June) 1942.

38. Chana, C. P.: Los reacciones serologicas de la lues y su interpretacion en los casos de linfogranulomatosis venerea, *Rev. méd. de Chile* **69**:715 (Nov.) 1941.

39. Brown, T. M., and Nunemaker, J. C.: Rat Bite Fever: A Review of the American Cases with Reevaluation of Etiology; Report of Cases, *Bull. Johns Hopkins Hosp.* **70**:201 (March) 1942.

40. Kahn, R. L.: A Serologic Verification Test in the Diagnosis of Latent Syphilis, *Arch. Dermat. & Syph.* **41**:817 (May) 1940.

41. Chargin, L., and Rein, C. R.: The Kahn Verification Test: An Appraisal of the Test Based on Clinical and Serologic Evidence, *Arch. Dermat. & Syph.* **44**: 1031 (Dec.) 1941.



themas, pinta, malaria and leprosy. These tests were all performed in Kahn's laboratory without benefit of clinical data.

In the group of 349 syphilitic patients, who had received varying amounts of treatment, the verification test gave the syphilitic type reaction in 100 per cent of patients with strongly positive serodiagnostic reactions, in 76.5 per cent of those with weakly positive reactions and in 40.2 per cent of those with doubtful reactions. Of 267 presumably nonsyphilitic persons, the result of the verification test was negative in 265. In the group with questionable reactions 32.7 per cent gave a syphilitic type of verification reaction. The highest incidence of the general biologic type of reaction was found to be associated with doubtful serodiagnostic reactions in all groups. Agreements as well as discrepancies were observed in serums subjected to repeated verification tests.

The authors' appraisal indicates a sufficient number of discrepancies in the results of the test to cast doubt on its ultimate efficacy in "verifying" the fact of syphilitic infection.

Seeking a differential method whereby the specificity of the serodiagnostic test for syphilis can be increased, Rytz<sup>42</sup> describes a method in which reagin is separated from the bulk of serum protein by precipitation with a weak solution of copper sulfate. Reagin thus remains in solution, together with only small quantities of serum protein. Rytz believes that "protein lability" is a factor in false positive serologic reactions, and he seeks by removal of serum protein to make a more specific test. Preliminary results obtained with the technic are given.

#### PREVALENCE

Clark and Turner<sup>43</sup> have studied the prevalence of syphilis among specific age groups of Negroes in the enumerated population of the Eastern Health District of Baltimore. The two age groups chosen were 20 to 24 years and 35 to 39 years. From a study of existing records and from examinations made during the course of the study minimum prevalence rates were established. These rates were: ages 20 to 24, men 19.7 per cent and women 31.6 per cent; ages 35 to 39, men 33.6 per cent and women 40.4 per cent. Among women of both age groups the rate for single persons was higher than for married ones, but no such difference was noted among men. Rates were higher among those who had not attended high school and among those who

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42. Rytz, F.: Specificity in the Serodiagnosis of Syphilis: A Differential Method, *Am. J. Clin. Path.* **12**:166 (March) 1942.

43. Clark, E. G., and Turner, T. B.: Study of the Prevalence of Syphilis Based on Specific Age Groups of an Enumerated Population, *Am. J. Pub. Health* **32**:307 (March) 1942.

were unemployed. The authors discuss in detail the technic of their carefully planned method of investigation and express the belief that it is susceptible of application in subsequent years and that the prevalence rates so obtained will afford a reliable index of the trend of syphilis in the community studied.

During the course of an epidemiologic study of leprosy in the Virgin Islands of the United States in 1939 and 1940, more than 70 per cent of the inhabitants of the island of St. Thomas and more than 95 per cent of the population of a rural area on the island of St. Croix were examined in clinics. In all, there were 10,000 persons on whose serum serologic tests for syphilis were made, and this number represented about 60 per cent of the inhabitants of the two areas. Of the persons tested, reports Saunders,<sup>44</sup> 1,495 (15.7 per cent) were found to have positive serologic reactions for syphilis. Approximately 70 per cent of the population are Negroes; more than 20 per cent are of mixed Negro and white strains, and less than 10 per cent are pure white or Puerto Ricans. Eighteen per cent of the Negroes, 14.6 per cent of the mulattos, 7.4 per cent of the Puerto Ricans and 4 per cent of the white persons tested had positive serologic reactions. Among female Negroes the positive reactions increased earlier in life and reached a peak of about 27 per cent in the age group between 40 and 50 years. The peak in the male, of about 36 per cent, was reached about a decade later.

According to Harrison,<sup>45</sup> the incidence of syphilis in England and Wales is decreasing despite war conditions. Factors in this declining incidence include diminution of traffic with foreign countries, the relatively low rate attained prior to the outbreak of war, the existing system of treatment centers and the thorough treatment given to men in the armed forces, now a substantial proportion of the male population.

Since the outbreak of war in Europe in September 1939, Burow<sup>46</sup> reports there has been a progressive increase in the incidence of venereal disease among alien seamen examined at the New York Quarantine Station. Sailors from the Scandinavian countries, denied return to their homeland, where venereal diseases were relatively rare; where prompt treatment was sought, received and enforced, and where home influences placed a restraint on promiscuous sexual conduct, have

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44. Saunders, G. M.: Prevalence of Syphilis in the Virgin Islands of the United States: Results of a Serologic Survey, *Arch. Dermat. & Syph.* **45**:506 (March) 1942.

45. Harrison, L. W.: The Present Trend of Incidence of Venereal Diseases in England and Wales, and Methods of Control, *Brit. J. Ven. Dis.* **17**:249 (July-Oct.) 1941.

46. Burow, F. P.: Increase of Venereal Diseases Among Foreign Merchant Seamen Examined at the Port of New York, *Ven. Dis. Inform.* **23**:11 (Jan.) 1942.

shown the greatest increase in venereal infections. There is evidence to show that when vessels have made Latin American cities ports of call, the incidence of syphilitic infection is higher; although seamen from South America had lower venereal disease rates than Scandinavian, British or German personnel.

#### EPIDEMIOLOGY OF SYPHILIS

*Early Syphilis.*—Webster and Shelley<sup>47</sup> report the results of contact investigation of 269 patients with early syphilis admitted to the Syphilis Clinic of the New York Hospital during the years 1937 to 1940, inclusive. These 269 patients named 663 contacts (2.46 contacts per patient). Of all contacts named, 81.7 per cent were found and examined, and of all examined contacts, 31.8 per cent had infectious syphilis. This is a ratio of 83.3 new patients with infectious syphilis per hundred original patients. The investigation of the 269 original patients yielded 224 more patients with infectious syphilis. The approximate cost of carrying out these investigations was \$18 per contact found to have infectious syphilis. The authors conclude that an epidemiologic investigation of patients with infectious syphilis appeared to be feasible and financially possible in a large metropolitan area.

*Acquired Syphilis in Children.*—The public health and epidemiologic significance of acquired syphilis in childhood and adolescence is emphasized by Dyar and Goodwin.<sup>48</sup> Their study of acquired syphilis in 16 colored and 3 white children under 14 years of age revealed a surprising amount of sexual activity in the prepubescent period. Investigation of the sexual and the household contacts of 10 source patients led to the discovery of 14 instances of infectious syphilis and 6 instances of latent syphilis not previously recognized. A superficial survey of the socioeconomic factors in the households of the infected children suggests that crowded living conditions, unemployment and the accompanying economic stress are associated with the spread of acquired syphilis to a younger age group than is usually affected.

*Syphilis in Negroes.*—The high incidence of syphilis in Negroes is a matter of common knowledge. There is reason to believe that lower educational standards are in part responsible. Cornely<sup>49</sup> reports that 22 of 40 Negro colleges include in their entrance health examinations a serologic test for syphilis, a ratio eight to ten times higher than that

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47. Webster, B., and Shelley, E. I.: Epidemiology of Primary and Secondary Syphilis in New York City, *Am. J. Pub. Health* **31**:1199 (Nov.) 1941.

48. Dyar, R., and Goodwin, M. H.: Acquired Syphilis in Childhood and Early Adolescence, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:704 (Nov.) 1941.

49. Cornely, P. B.: Syphilis Case-Finding Program in Negro Colleges, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:713 (Nov.) 1941.

in white colleges. Tests made on 24,347 students over a period of five years show a rate of positive serologic reactions of 42 per thousand, which is ten to twenty times higher than the rate in white colleges. The author notes that a sizable group of colleges do not provide facilities for the treatment of their students.

"Syphilis in the Negro" is the title of a brochure by Hazen,<sup>50</sup> which was published as a supplement to *Venereal Disease Information* and so is available for widespread distribution. It provides a summary of the incidence, prevalence and trend of syphilitic infection in Negroes, including pathologic changes, clinical course, diagnosis, treatment and prophylaxis. In the introductory statements Hazen says:

One cannot escape the observation that the greatest single reservoir of syphilis in America is the Negro. But when one seeks an explanation through prevalence surveys in various areas where the Negro comprises a significant proportion of the population, he finds the problem transcends racial boundaries. Where the Negro syphilis rate is high, the rate in the white group as well is likely to be unusually high. He finds, by comparison of these areas with those having lower rates for both Negro and white, that a less vigorous effort has been made to control the disease. Treatment facilities in the areas of high prevalence prove to have been inadequate and largely inaccessible. Likewise, the public is not as well informed on the value of early and adequate treatment in arresting the disease and in preventing its spread. And he reaches the conclusion that the most outstanding characteristic in these areas of high prevalence is a low economic status in a large proportion of the population.

*Contact Investigation.*—Sweeney<sup>51</sup> describes the general methods of obtaining from patients with early syphilis the names of extramarital sexual contacts and the method of approach both to extramarital sexual contacts and to household contacts for the purpose of persuading them to be examined. Success in obtaining contact information depends on securing the cooperation of the patient, for a well informed, tactfully handled patient is usually willing to divulge this information, provided he is assured that his own name will not be revealed to the contacts. The author believes the general approach to sexual contacts differs somewhat according to the age, the marital status and the economic situation of the individual contact, and she describes in detail effective procedures for each contingent situation.

#### SYPHILIS AND THE WAR

*Wartime Problems of Civilian Public Health Agencies.*—As an example of the responsibility placed on civilian public health agencies in areas adjacent to military concentrations Rowntree, Fischbach and

50. Hazen, H. H.: Syphilis in the Negro, Ven. Dis. Inform., 1942, supp. 15.

51. Sweeney, A.: Methods of Contact Investigation Employed by the Syphilis Clinic of Vanderbilt University Hospital, Ven. Dis. Inform. 23:137 (April) 1942.

Leavell<sup>52</sup> cite their work in Louisville, Ky., which city is experiencing a sudden and marked increase in population because of war industry and the establishment of an Army post, Fort Knox, 30 miles (48 kilometers) away. This growth has brought about congestion and overcrowding. There are many new small bars, cafes and lunchrooms which provide both food and drink. Also, there is overcrowding in cheap rooming houses and low rent quarters. All these factors have a bearing on the civilian and military venereal disease problem and have necessitated more extensive measures and new procedures for control, which are discussed in detail.

*Prostitution.*—In readable, graphically pictoillustrated pamphlet form Broughton<sup>53</sup> outlines the problem of prostitution in time of war. He points out why segregation and inspection of prostitutes are not the answers to this problem and concludes that a determined effort at repression is the proper solution. Cooperation between the Army, the Navy, Public Health Service, the Social Protection Section of the Federal Security Agency and the public health and police officials in local communities is essential to adequate repression. In areas where local authorities do not act, the Federal Bureau of Investigation may be called on to do the necessary police work under authority of the May Act, passed by Congress in 1941.

Aware of the discrepancy in the reported incidence of contraction of venereal disease from prostitutes in different sections of the country, Johnson<sup>54</sup> has studied the contacts of soldiers at Fort Bliss, Texas. This military cantonment is situated outside the city limits of El Paso (population, about 100,000). El Paso is within walking distance of Juarez, Mexico (population, approximately 50,000). In both El Paso and Juarez houses of prostitution were legal and under police protection at the time this study was begun. The report includes 526 instances of venereal disease in soldiers, of which 424 were gonorrhea, 40 early syphilis and 62 chancroid.

Prior to the closing of the houses of prostitution in El Paso 73.7 per cent of all infections were contracted from prostitutes, 16 per cent from "pick-ups" in dance halls and bars and 10.3 per cent from friends or other sources. Fifty-six per cent of the soldiers contracted venereal infections in El Paso and 24.4 per cent in Juarez.

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52. Rowntree, G. R.; Fischbach, C. M., and Leavell, H. R.: Venereal Disease Control in the National Defense Program, *South. M. J.* **35**:187 (Feb.) 1942.

53. Broughton, P. S.: Prostitution and the War, Public Affairs Pamphlet, no. 65, New York, Public Affairs Committee, Inc., 1942.

54. Johnson, B., Jr.: Role of Open Houses of Prostitution in the Spread of Venereal Diseases in a South-Western Cantonment Area: Preliminary Report of an Epidemiologic Study, *Ven. Dis. Inform.* **23**:15 (Jan.) 1942.

After the closure of the nine legal houses of prostitution in El Paso, there was a decrease in the incidence of venereal disease contracted in brothels. During this period of the study only 51.6 per cent of infections were referable to such houses, whereas there was a definite increase in the number of soldiers infected through "pick-ups" (30.6 per cent). The incidence of disease contracted in Juarez also increased above that contracted in El Paso. It therefore seems evident that the main source of infection is still the commercial prostitute operating in a brothel and that the chief place of infection has shifted from El Paso to Juarez.

*Syphilis Among Selectees.*—In the present war for the first time an effort has been made not only to examine all men for venereal disease but to perform routine serologic tests for syphilis on them. The results of this huge serologic survey, which furnish the most accurate estimation yet available of the prevalence of syphilis throughout the nation, have been reported from many states, chiefly in the respective state medical journals.

A summation of the findings throughout the nation has been prepared by the United States Public Health Service and reported by Vonderlehr and Usilton.<sup>55</sup> These authors have calculated the incidence of syphilis among the first 1,051,985 selectees, who were examined between November 1940 and April 1941. The incidence is based entirely on the results of serologic tests for syphilis which were routinely performed on all selectees. The greatest prevalence of syphilis was reported by Florida and South Carolina, with rates of 170.1 and 156 syphilitic men per thousand selectees, respectively. The lowest rate was reported by New Hampshire, 5.8 per thousand. Seven Southern states and the District of Columbia reported rates in excess of 100 per thousand. The rate for Negroes was in each state higher than the rate for white men, and there were indications that high rates among the white selectees were coincidental with the high rates among the Negroes. The average rate for the country at large was 45.2 per thousand.

The authors present tables expressing the rates in terms both of white and of Negro selectees for each state and the prevalence of syphilis among selectees classified by the size of the community in which they reside.

Statistics of the Selective Service System<sup>56</sup> indicate that of the first 2,000,000 men examined, 900,000 were classified as unfit for general military service because of physical or mental defects. Of those unqualified, 57,000 (6.3 per cent) were rejected because of venereal disease.

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55. Vonderlehr, R. A., and Usilton, L. J.: *Syphilis Among Selectees and Volunteers: Prevalence in First Million Men Examined Under the Selective Service Act of 1940*, J. A. M. A. **117**:1350 (Oct. 18) 1941.

56. *Analysis of Reports of Physical Examination*, Medical Statistics Bulletin 1, National Headquarters, Selective Service System, Nov. 10, 1941.

The syphilis rate was 27.6 per thousand men examined, the vast majority of diagnoses being based on serologic evidence alone.

The apparent discrepancy between the incidence of positive serologic reactions in selectees described by Vonderlehr and Usilton and the much lower incidence indicated by Selective Service rejections obviously depends on different methods of statistical approach.

*Rehabilitation of Men Rejected Because of Venereal Disease.*—The rehabilitation of rejected examinees is discussed by Reynolds,<sup>57</sup> who describes the system of epidemiologic follow-up and medical care of men rejected by Selective Service agencies in Pennsylvania because of venereal disease. Those found infected were reported to the clinic nearest their home for treatment and contact investigation. Of 1,370 patients investigated, 704 were given treatment in clinics and 355 by private physicians. Sixty contacts were reported, of whom 23 were found to be infected.

Dyar<sup>58</sup> describes the program set up in San Joaquin county, Calif., for utilizing information pertaining to serologic tests for syphilis among selectees. A record of all tests is maintained in the state laboratory, and the names of all persons with positive or doubtful reactions are referred to the State Health Department. Reports are transmitted to the local draft board via the examining physician, the names being checked against a master file. Follow-up consists of a notification card, a visit and subsequently a personal interview. The prevalence rate of syphilis among men examined by Selective Service agencies was: white men, 3.4 per cent; Negroes, 27.3 per cent; Chinese, 12.1 per cent, and Japanese, 2.3 per cent. Of 129 registrants with positive or doubtful serologic reactions, 46 were referred to public clinics or private physicians as having previously unrecognized syphilis, 33 previously known to have syphilis were referred for resumption of treatment, 21 were under active treatment and 8 were considered adequately treated. Four men were referred to clinics in a different locality; 12 were never located, and 5 were declared nonsyphilitic.

Vonderlehr,<sup>59</sup> discussing the status of the venereal disease control program in times of mobilization, offers a plan to provide effective facilities under the Selective Service System for all men found infected with venereal disease. The opportunity for contact investigation of these men with known syphilis should not be neglected. For the improvement

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57. Reynolds, C. R.: Rehabilitation and Follow-Up of Selective Service Men Rejected for Military Service, *Mil. Surgeon* **90**:232 (March) 1942.

58. Dyar, R.: Syphilis in Selective Service Registrants: Determination of Prevalence and Plan of Rehabilitation of Proven Cases, *Ven. Dis. Inform.* **23**:43 (Feb.) 1942.

59. Vonderlehr, R. A.: Present Status of the Venereal Disease Control Program in Mobilization and National Defense, *Am. J. Pub. Health* **31**:1027 (Oct.) 1941.

of the entire venereal disease control program, especially as it relates to the present emergency, Vonderlehr recommends:

(1) Intensive training in the epidemiology of the venereal diseases of otherwise qualified new and old follow-up personnel, especially in contact tracing and case holding . . .

(2) The development of measures to discourage the present tendency of treatment sources to over-treat patients with late and late latent syphilis, especially when such treatment sources fail to provide adequate therapy and follow-up for patients with early infectious venereal diseases.

*Syphilis in the Armed Forces.*—Brown<sup>60</sup> says that as a result of the present national emergency the problems of social hygiene and the mechanisms of control of venereal disease have assumed a new significance for the armed and the industrial defense forces of the nation. In this paper he describes the problems confronting the Navy at this time of rapid expansion. When this paper was written, there were approximately 150,000 to 200,000 industrial workers employed in the various Navy yards. This already exceeds the number of industrial workers in Navy yards during the first World War. There is also reason to believe that the military personnel of the Navy will also exceed that of the first World War.

No emphasis need be placed on the extreme importance of control of venereal disease among naval industrial civilian personnel, as well as among naval forces. If a high rate of venereal disease exists, this will tend to cause wastage of such workers, as well as retard the construction program.

The problems of venereal disease prevention confronting the Army and the Navy are chiefly administrative and fall into two divisions: those directly under military jurisdiction, and those under the jurisdiction of the civil authorities, the United States Public Health Service and the state and local health and police agencies, as well as voluntary organizations, headed by the American Social Hygiene Association. By far the most pressing problems are presented in the second division, since the source of venereal infection of military personnel is in the civilian population.

There is considerable variation in the incidence rate of gonorrhea in various naval ports. Twenty cities were involved in this study, the average rates per thousand of personnel varying from 106 for New Orleans to 11.6 for Annapolis, Md. San Francisco had the second highest rate, 60.3, and New York the eleventh, 28.1. These differences suggest considerable variation in the status of venereal disease hazards among the civilian populations of the different localities.

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60. Brown, E. W.: The Navy and Social Hygiene in National Defense, War Med. 1:511 (July) 1941.



As to the control of venereal disease in the Navy, there is a fivefold program in force:

. . . (a) educational; (b) prophylactic; (c) disciplinary; (d) recreational, and (e) medical. A sixth line of action falls under legal and protective activities for the reduction of prostitution and prevention of delinquency in areas adjacent to naval concentrations primarily under civil direction but with the cooperation of naval authorities.

Each of these measures is discussed in some detail.

As to the sixth point in the program, the extreme importance of the agreement by the War and the Navy Department and other agencies for the control of venereal disease is recognized, and the Secretary of War and the Secretary of the Navy have asked the cooperation of the Surgeon General of the United States Public Health Service in developing the best facilities possible for the control of venereal disease among civilians. Although the principles of venereal disease control had been determined, the division of responsibility among these various units had not been definitely established.

In July 1940 the Navy Department directed the naval medical officers to report all sources of venereal infection to the local health authorities. The local and the state health agencies are reporting contacts of enlisted men with infected civilians to senior medical officers. Those procedures are of tremendous importance as aids in case finding.

The task confronting the civilian authorities may be considered from two angles: first, the control of infection among prostitutes and, second, the reduction of prostitution. In spite of the fact that prostitution cannot be entirely eliminated, it can be controlled within certain limits. There are existing laws in most localities under which the state and municipal health and police authorities can place under arrest, quarantine or insist on treatment of prostitutes known to have or suspected of having a venereal disease.

Two examples are given of what may be accomplished by the effective coordination of plans between the Army and the Public Health Service, on the one hand, and the local authorities with the aid of the American Social Hygiene Association, on the other. In the first instance during Army maneuvers in Minnesota 40,000 men were in a given area for six weeks. During this time there were only 6 infections with gonorrhea, or less than 1 per 6,000 men, and no cases of syphilis were reported. In the second instance a control program was applied to a concentration of troops in an area lying in two adjoining Southern states. There was the usual influx of prostitutes to the extramilitary zone, and the venereal disease rate rose to about 62 per thousand. However, as a result of a coordinated program adopted, this rate was reduced by half within four months.

A significant study of syphilis in the Navy has been made by Mast.<sup>61</sup> This study, documented by extensive statistical material, covers the ten year period from 1929 to 1938, inclusive. Mast concludes:

(1) The highest new admission rates for syphilis were found among the Forces afloat, and Forces ashore stationed in foreign territory.

(2) The type of ship in relation to the size of the medical department has no bearing on the syphilis rates. The location and activity (movement) have a direct relationship to the rate.

(3) The admission rates for syphilis are highest where the economic and social standards are lowest; as local conditions approach those found in the United States, the local rates tend to reach the United States level.

(4) The level of intelligence and education required for an occupation is probably the most important single item influencing the rates for syphilis in the occupational groups. The greater the intelligence required, the lower the rate. (One exception is apprentice seamen who spend about six months of the first year in the training station.)

(5) The effect of sex education is not conclusive.

(6) Measures for the control of syphilis should be augmented in the Forces afloat who are stationed in the Asiatic area, and among those who are constantly en route, such as the Naval Transportation Service. They should also be further strengthened where Forces are serving ashore in foreign countries.

(7) Measures for the control of syphilis must be concentrated on the men who have had several years of naval service, the highest rate being in the third enlistment period.

Youngkin<sup>62</sup> discusses the educational program of the Navy with respect to venereal disease on the basis of a questionnaire circulated among the crew of a naval vessel. A surprising lack of knowledge and distortion of fact was found, despite the fact that lectures on syphilis and its prophylaxis had been given. Youngkin believes the primary medium for an educational program should be the printed page, supplemented by such additional types of instruction as discussion groups and motion pictures.

Angwin<sup>63</sup> considers "station" prophylaxis objectionable because of the excessive time lag between venereal exposure and treatment. To provide early prophylaxis, the author recommends a readily portable packet containing condoms, soap and mild mercurous chloride ointment.

*Venereal Disease Control Officers in the Armed Services.*—During World War I it was demonstrated that the adequate control of venereal diseases required the employment by the armed forces of medical

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61. Mast, G. W.: Ten Year Study of Syphilis in the United States Navy (1929-1938 Inclusive), Thesis, Johns Hopkins University, 1942.

62. Youngkin, C. K.: Venereal Disease Education in the Navy, U. S. Nav. M. Bull. **39**:535 (Oct.) 1941.

63. Angwin, W. A.: Soap and Water as a Venereal Disease Prophylactic, Mil. Surgeon **90**:439 (April) 1942.

personnel who would devote full time to this work. Under this system the venereal disease rate in the Army during the first World War fell off noticeably instead of doubling, as in every previous conflict.

The armed services during World War II have utilized this experience and are now <sup>64</sup> training medical officers with clinical and public health experience and assigning them as venereal disease control officers. These men will function within the Army and the Navy, maintaining liaison with governmental and civilian police and public health agencies which are likewise concerned.

Proposed duties include improvement of the educational program, cooperation to provide adequate recreational facilities, maintenance of adequate facilities for prophylaxis, provision for the detection of cases of early disease, supervision of facilities for diagnosis and treatment of military personnel, close cooperation with other agencies and the collection and analysis of morbidity data.

#### SYPHILIS AND INDUSTRY

The growing tendency of industry to promote mass serologic testing for syphilis and the injustices to employees which have at times resulted therefrom have been discussed editorially by Moore.<sup>65</sup>

In his opinion,

It is most important that persons shall not be employed (a) who may transmit an infectious disease to others; (b) whose physical disabilities may create increased industrial hazard of injury to themselves or others; or (c) whose physical disabilities may result, whether from injury or illness, in an increased actuarial risk of disability benefits, pensions, or death benefits.

Because the United States Civil Service Commission is the largest employer in the nation, its policy toward applicants with syphilis has been watched closely by private industries. Since January 1939 the United States Public Health Service has cooperated with the Commission to bring its policy into line with modern knowledge. Anderson <sup>66</sup> reviews the achievements to date and the recommended objectives for the future.

Brown <sup>67</sup> points out that the importance of syphilis as a government industrial problem has been increased by the rapid expansion of industry engaged in war work. On July 1, 1941 the combined civil personnel

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64. Venereal Disease Control Officers, *J. A. M. A.* **118**:824 (March 7) 1942.

65. Moore, J. E.: Syphilis and Employment, editorial, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:378 (March) 1942.

66. Anderson, O. L.: The Policy of the United States Civil Service Commission Towards Applicants with Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:265 (May) 1942.

67. Brown, E. W.: Protection of Workers in Government Defense Industries from Venereal Diseases, *War Med.* **2**:246 (March) 1942.

under the control of the Army and the Navy was approximately 493,000. The author indicates that venereal disease control measures applicable to the armed services must be modified to fit industrial needs. A proposed program for syphilis control in naval government industry is outlined to include administrative approval by the Civil Service Commission and the Navy, education both of executives and of laborers, preemployment and reemployment serologic tests, disposition of infected workers in accord with modern knowledge, confidential records and repression of prostitution. Brown believes that federal government industry should take the initiative in venereal disease control.

In the formulation of an industrial syphilis control program Gillick and Buxell<sup>68</sup> recommend (1) a policy-making group, consisting of competent representatives both of the employer and of the employees, together with experienced medical consultants; (2) an educational campaign to precede the institution of the program; (3) voluntary participation by employees; (4) maintenance of confidential relations; (5) individualized decisions by competent specialized medical consultants as to employment, continued employment and changes to less hazardous positions; (6) adequate examinations; (7) individualized treatment, to be given within industry only when adequate treatment cannot be obtained elsewhere, and (8) integration of the industrial program with the community's program.

Some information as to the present status of syphilis control in industry was obtained by McGrath,<sup>69</sup> using the questionnaire method. Of 175 industrial concerns questioned, 60 per cent include a serologic test in at least some of their medical examinations and only 4 per cent discharge infected employees. Twenty per cent retain their old workers when infection is found but refuse to hire new workers who are syphilitic, and 73 per cent retain all employees with positive reactions and insist that they receive adequate treatment. Employees are not treated in the majority of plants but are sent to private physicians.

#### DRUGS

*Chlorarsen.*—This is a mixture of 3-amino-4-hydroxyphenyldichlorarsine hydrochloride with sodium citrate, believed to be identical with mapharsen on solution and after intravenous injection. Tompsett and his co-workers<sup>70</sup> have studied the mixture in a series of animal

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68. Gillick, F. G., and Buxell, J.: A Syphilis Control Program for Industry and Its Integration with the Community Program, *Indust. Med.* **10**:548 (Dec.) 1941.

69. McGrath, E.: Coal Mine Health Meeting, *J. Social Hyg.* **27**:441 (Dec.) 1941.

70. Tompsett, R. R.; Downs, W. G.; McDermott, W., and Webster, B.: The Use of Chlorarsen in the Treatment of Syphilis, *J. Pharmacol. & Exper. Therap.* **73**:412 (Dec.) 1941.

experiments and subsequently in clinical use in 171 patients. The compound is considered by them to be safe and effective in the treatment of syphilis as judged by:

. . . (1) rapid production of darkfield negativity of early lesions; (2) prompt healing of early lesions; (3) effectiveness in producing seronegativity in early syphilis; (4) low percentage of relapses; (5) low incidence of abnormal spinal fluids in early syphilis; (6) absence of severe immediate reactions to its administration and relatively low number of reactions in general.

Altire and co-workers<sup>71</sup> have also tested this mixture for toxicity and as a trypanocidal and a spirocheticidal agent in animals. When injected intraperitoneally in mice or intravenously in rats, chlorarsen was found to have a toxicity approximately the same as that of mapharsen. Its trypanocidal activity against *Trypanosoma equiperdum* in rats and its spirocheticidal action, whether in vitro or in vivo in rabbits, were found to be at least as great as those of mapharsen.

*Oxiarsolan (Arsenoxide Hydrochloride).*—Another arsenoxide comparable to mapharsen (arsenoxide hydrochloride [oxiarsolan]) has been developed at the Bacteriologic Institute of Chile. The chemical features of this drug have been described by Ceruti<sup>72</sup> and its clinical applicability to massive dose arsenotherapy by Infante.<sup>73</sup> The therapeutic efficacy and the toxicity of this compound are similar to those of mapharsen.

*Colloid and Crystalloid Fractions of Arsenicals.*—Wright and Rodman<sup>74</sup> have investigated the comparative distribution and retention of the whole drug and the crystalloid and the colloid fraction of arsphenamine and neoarsphenamine in the tissues of the rat. At intervals after intravenous administration of the drugs the animals were killed and various tissues analyzed. The results indicate that the colloid fraction either of arsphenamine or of neoarsphenamine is long retained in the body, whereas the crystalloid fraction is rapidly eliminated.

*Experimental Study of Arsenical Compounds.*—Having previously studied the effects on toxicity and spirochetocidal activity of the introduction of simple substituent groups into phenylarsenoxide, Eagle and his co-workers<sup>75</sup> now report the effect of multiple substituents. The effect

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71. Altire, W. E.; Rake, G.; Van Dyke, H. B., and Walker, H. A.: Experimental Studies on the Value of Chlorarsen as an Antisyphilitic, *J. Bact.* **43**:645 (May) 1942.

72. Ceruti, L.: Aspectos químicos de los arsenicales orgánicos, *Rev. méd. de Chile* **69**:724 (Nov.) 1941.

73. Infante, L.: El arsenóxico en clínica, *Rev. méd. de Chile* **69**:729 (Nov.) 1941.

74. Wright, H. H., and Rodman, F. B.: Comparative Distribution and Retention of Crystalloid and Colloid Fraction of Arsphenamine and Neoarsphenamine, *Proc. Soc. Exper. Biol. & Med.* **49**:229 (Feb.) 1942.

75. Eagle, H.; Hogan, R. B.; Doak, G. O., and Steiman, H. G.: The Effect of Multiple Substituents on the Toxicity and Treponemicidal Activity of Phenylarsenoxide, *J. Pharmacol. & Exper. Therap.* **74**:210 (Feb.) 1942.

on potential therapeutic utility (rate of spirocheticidal activity in vitro: mouse toxicity) could not regularly be anticipated from the effect of the groups acting singly. In general, except for certain of the aminophenols combinations of two or three groups were no more favorable, and often were distinctly less favorable, than the best one of the constituent groups.

In a survey preliminary to further studies with arsenicals used in syphilotherapy, du Pont, Ariel and Warren<sup>76</sup> have determined the distribution of arsenic in the bodies of normal rabbits, using radioactive arsenic as a tracer, or tag, for a simple arsenic salt, sodium dihydrogen arsenate ( $\text{NaH}_2\text{AsO}_4$ ). The authors summarize their experience as follows:

1. The distribution of radioactive arsenic when injected intravenously as sodium arsenate in subtoxic doses is relatively nonuniform.

2. The rapid excretion by the urine seems to be independent of the period of highest concentration in the kidney.

3. Both concentration and total content are high in liver, kidney, and lungs during the first three hours after injection, after which the values in these organs rapidly fall off.

4. While the concentration is relatively low in muscle, bone, and skin, the total content is relatively high; thus these organs are the main storage sites in the body.

5. The concentrations in spleen, bone marrow, stomach, and intestinal walls reach fairly high levels but the duration of these high levels is relatively short.

6. The cancellous bone does not seem to fix arsenic after a single, subtoxic dose any more permanently than does any other tissue.

7. At the dosage level used (2 mg. total) there is very little radioactive arsenic detectable in any organ after one week.

8. Tumor takes up arsenic in a significant concentration and loses it by the fourth day. Tumor destroyed by roentgen radiation seems to take up little of the arsenic in the few cases studied.

This novel method of determining the distribution and concentration of arsenic in tissues and body fluids gives promise of significant advances to knowledge of arsenotherapy.

*Bismuth Ethyl Camphorate.*—Alexander and Schoch<sup>77</sup> report the results of treating 26 patients with early syphilis with bismuth ethyl camphorate. This preparation is a liposoluble bismuth salt of ethyl camphoric acid, having 23.47 per cent bismuth, or 40 mg. of elemental bismuth per cubic centimeter. Only patients with primary or secondary syphilis with spirochetes demonstrable by dark field examination were

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76. du Pont, O.; Ariel, I., and Warren, S. L.: The Distribution of Radioactive Arsenic in the Normal and Tumor-Bearing (Brown-Pearce) Rabbit, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:96 (Jan.) 1942.

77. Alexander, L. J., and Schoch, A. G.: Bismuth Ethyl Camphorate: Its Use in Twenty-Six Cases of Early Syphilis, *Arch. Dermat. & Syph.* **45**:876 (May) 1942.

chosen for these studies. Each patient was given 2 cc. of bismuth ethyl camphorate intramuscularly at seven day intervals. The authors believe on the bases of disappearance of surface spirochetes, healing of lesions and serologic response that bismuth ethyl camphorate given in this dosage is a valuable adjunct to the arsphenamines in the treatment of syphilis.

*Sobisminol*.—Batchelor, Murrell and Thomson<sup>78</sup> report a limited experience with the oral use of sobisminol mass. They believe that sobisminol mass can and should have a place in the treatment of those persons who cannot attend regularly for injection therapy—e. g., seamen and those patients who are intolerant of arsenic and in whom for any reason injection therapy is contraindicated. With their suggestion that the drug is also indicated in patients “who show persistently positive serological tests in spite of long continued parenteral treatment,” few physicians in this country would agree.

The successful oral use of sobisminol mass in the treatment of syphilis has stimulated the development of closely related bismuth complexes as possible substitutes. A report by Van Winkle and Hanzlik<sup>79</sup> gives the results of a study on the gastrointestinal absorption and the toxicity of a new compound prepared from the same ingredients which enter into the composition of sobisminol mass. This compound was prepared by Miller, whose original objective was to determine the chemical nature of sobisminol mass. He was unable to isolate any pure products from the reaction between sodium bismuthate and triisopropanolamine in propylene glycol. He therefore carried out a reaction between sodium bismuthate and triisopropanolamine in xylene instead of in propylene glycol and was able to obtain a definite chemical compound, which has been named sodium bismuthyltriisopropanolamine. This same compound was produced when bismuth hydroxide was used instead of the bismuthate. The compound prepared with the hydroxide has been used in the present experiments.

So far as the possible use of this drug for the treatment of syphilis was concerned, the results were disappointing. The drug was introduced into ligated loops of the small intestines of laparotomized cats, and evidence of absorption was determined by a positive reaction for bismuth in the urine. As a control, sobisminol solution was introduced into the ligated loops of the same cats after the completion of the test with the new drug. After the introduction into the small intestine of 60 and

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78. Batchelor, R. C. L.; Murrell, M., and Thomson, G. M.: Oral Medication by Sobisminol in Treatment of Syphilis, *Brit. M. J.* **2**:541 (Oct.) 1941.

79. Van Winkle, W., Jr., and Hanzlik, P. J.: A New Bismuth Compound Identical in Chemical Origin with Sobisminol Mass, *Arch. Dermat. & Syph.* **45**: 478 (March) 1942.

100 mg., respectively, of the new bismuth preparation, no bismuth could be detected in the urine. However, after the introduction of 60 mg. of sobisminol solution, bismuth was readily demonstrated in the urine. Since the drug was not absorbed, it was nontoxic to white rats.

*Absorption of Compounds Containing Bismuth.*—Sproull and Lehman<sup>80</sup> have studied the factors influencing the absorption of water-soluble compounds containing bismuth from muscle and from the intestinal mucosa. (The influence of such factors as  $p_H$ , apparent bismuth ion concentration [stability toward chemical reagents] and salt concentration was investigated.) The rate of intramuscular absorption at comparable hydrogen ion concentrations was found to be a function of the chemical stability. The order of absorption, beginning with the most rapidly absorbed compound, was thio-bismol, sodium bismuth triglycollamate, sodium bismuth cevitamate, sodium bismuth citrate, potassium bismuth saccharate, bismuth and potassium tartrate with sucrose and bismuth and potassium tartrate alone. A change in  $p_H$  away from the physiologic level was found to cause a small but significant decrease in the absorption rate of sodium bismuth triglycollamate, but there was no significant change in the absorption rate of potassium and bismuth tartrate. Absorption after oral administration was also found to be a function of the chemical stability, but the relation was less pronounced and was modified in individual animals.

*Distribution and Storage of Compounds Containing Bismuth.*—Brown and Kolmer<sup>81</sup> have determined the distribution and the storage of bismuth in normal rabbits following the oral administration of sobisminol solution and water-soluble bismuth and potassium tartrate, controlling and comparing their results with intramuscular injections of both compounds in the same total dose in terms of elemental bismuth. They found that the urinary excretion of bismuth after oral administration of sobisminol solution was similar to that after its intramuscular injection, whereas with bismuth and potassium tartrate excretion was greater after intramuscular injection. The storage of bismuth after oral administration was similar to that after intramuscular injection. To obtain approximately equal bismuth storage in the tissues about thirty-five times as much bismuth had to be given orally as by intramuscular injection.

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80. Sproull, R. C., and Lehman, R. A.: A Study of Certain Factors Influencing the Absorption of Water Soluble Bismuth Compounds, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:166 (March) 1942.

81. Brown, H., and Kolmer, J. A.: Bismuth Excretion and Storage in Rabbits After the Oral and Intramuscular Administration of Sobisminol Solution and Water-Soluble Potassium Bismuth Tartrate, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:159 (March) 1942.



*Toxicity of Compounds Containing Bismuth Administered Intravenously.*—Sollmann and Seifter<sup>82</sup> report pharmacologic studies on three water-soluble compounds containing bismuth administered intravenously to experimental animals in which they compare the toxicity and the distribution of bismuth following acute injection with the results of slow injection by intravenous drip. The toxicity of sodium bismuth citrate and of sobisminol solution injected slowly was about half that following acute injection, but this was not noted with the more unstable thio-bismol. In rabbits the fatal dose by intramuscular injection was five to ten times higher than that given by slow intravenous injection.

In dogs the maximal concentration of bismuth in the blood following rapid injection was about four times that following intravenous drip, but by the end of two hours the concentration was similar with both methods. The product of average concentration and total time was about one-fifth higher with rapid, than with gradual, injection of a given dose. The concentration of bismuth in organs varied directly with the dose and inversely with the time elapsed since the injection, but the nature of the compound containing bismuth and the speed of injection had no significant bearing.

*Localization of Bismuth in the Kidney.*—Kroll and his co-workers<sup>83</sup> have demonstrated that the kidney of the normal rabbit does not accumulate amounts of thio-bismol sufficient for its roentgen visualization. On the other hand, in rabbits with preexisting renal damage injected thio-bismol could be demonstrated in the kidneys as radiopaque shadows in roentgenograms. The authors warn against the use of thio-bismol or similar compounds in the presence of damaged kidneys and draw attention to the possibility of demonstrating such damage roentgenographically after administration of a compound containing bismuth.

*Bismuth Transfer into Fetal Circulation.*—Thompson, Steadman and Pommerenke,<sup>84</sup> using spectrochemical methods, have shown that after oral administration of sobisminol mass there is a prompt appearance of bismuth in the maternal and the fetal blood and in the placenta and the umbilical cord. On the basis of the rapid transfer of bismuth to the fetal circulation after treatment with sobisminol mass, the authors consider this drug worthy of use in antepartum syphilotherapy.

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82. Sollmann, T., and Seifter, J.: Intravenous Injections of Soluble Bismuth Compounds: Their Toxicity, and Their Sojourn in the Blood and Organs, *J. Pharmacol. & Exper. Therap.* **74**:134 (Feb.) 1942.

83. Kroll, H.; Arens, R. A.; Mesirov, S.; Strauss, S. F., and Necheles, H.: Localization of Bismuth in the Kidney, *Surgery* **11**:810 (May) 1942.

84. Thompson, H. E.; Steadman, L. T., and Pommerenke, W. T.: The Transfer of Bismuth into the Fetal Circulation After Maternal Administration of Sobisminol, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:725 (Nov.) 1941.

## TREATMENT

As cleverly phrased by Osmond,<sup>85</sup>

The treatment of syphilis resolves itself essentially into two parts, that of early syphilis and that of late syphilis. . . . Early syphilis calls for a violent frontal attack, late syphilis for steady siege methods; the object of the former is to deal the spirochaete a knock-out blow; that of the latter to maintain the patient's resistance and prevent the invader from doing further damage.

Somewhat inconsistently, he expresses a preference for the "concurrent-intermittent" form of therapy, in which an arsenical and a compound containing bismuth are given at the same time in courses of ten weekly injections of each, the courses being separated by rest intervals of a few weeks—not the most "violent frontal attack" conceivable.

Marin<sup>86</sup> outlines the clinical course and therapy of early syphilis. Impressed by the number of patients who fail to complete routine treatment and by the results of massive dose arsenotherapy, the author recommends concentrated therapy combining weekly injections of neoarsphenamine and a compound containing bismuth for the first five months, followed by alternate courses of these drugs for one year after seronegativity is attained. The number of toxic reactions to this form of treatment compared favorably with the number occurring with the usual alternating therapy and were notably fewer than those occurring with the intravenous drip method. A five year period of surveillance following completion of treatment was considered adequate.

Midina<sup>87</sup> lists the causes of treatment resistance to antisyphilitic agents as reduced pharmacologic activity of the preparation, abnormal constitutional reaction of the host and strain variation in the spirochete. Of the three hypotheses, Midina considers the last to be most important, basing his conclusion on observations of treatment-resistant infections in marital partners.

## UNTOWARD EFFECTS OF TREATMENT

*Mortality Data.*—Further data regarding the incidence of toxic reactions to arsenicals have been compiled by Stephenson, Chambers and Anderson.<sup>88</sup> For the past sixteen years medical officers of the

85. Osmond, T. E.: The Modern Treatment of Syphilis, Practitioner **148**:257 (May) 1942.

86. Marin, A.: Traitement de la syphilis récente, Union méd. du Canada **71**:342 (April) 1942; The Treatment of Early Syphilis, Canad. M. A. J. **46**:334 (April) 1942.

87. Midina, A.: Sur la résistance pharmacologique de la syphilis, Minerva med. **2**:540 (Dec. 8) 1940; Praxis **31**:12 (Jan.) 1942.

88. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1940, U. S. Nav. M. Bull. **39**:605 (Oct.) 1941; Toxic Effects of Arsenical Compounds as Employed in the Treatment of Disease in the United States Navy, 1940, *ibid.* **40**:215 (Jan.) 1942.

Navy have been required to submit reports of the number of doses of arsenicals administered and the reactions therefrom. In this period 1,686,000 injections of various arsenicals have been given, with 51 fatal reactions, a ratio of 1 death to every 33,072 injections. Fifty of the 51 deaths were due to neoarsphenamine and 1 to arsphenamine. Two hundred and three thousand, one hundred injections of mapharsen have been given without fatality. Of 859 reactions recorded, 352 were ascribed to vasomotor phenomena and 326 to arsenical dermatitis.

In an extensive and timely review of fatal reactions to antisyphilitic treatment Hahn<sup>89</sup> reviews the literature and analyzes deaths due to treatment occurring at the Johns Hopkins Hospital. Hahn summarizes his study as follows:

1. The only long-term modern statistics concerning the mortality rate of antisyphilitic treatment are those of the United States Navy. Reliable data on the incidence of hemorrhagic encephalitis are not available.

2. During a twenty-seven-year period, there have been 22 deaths directly attributable to trivalent arsenicals administered in the Syphilis Clinic of the Johns Hopkins Hospital. The mortality rate was one in 1,250 treated patients, with one death to each 12,000 injections. During a sixteen-year period, there has been 1 death directly attributable to bismuth among 19,550 patients given 175,000 injections. There have been no fatalities from 17,000 injections of tryparsamide. In the three-year period 1937 to 1940, 4,800 patients have been given 64,000 injections of a trivalent arsenical without a fatality. The majority of these have been treated with mapharsen.

3. The mortality rate was three times as great for the negro as for the white patients, and twice as great for females as for males. The more frequent occurrence of acute yellow atrophy among women entirely accounted for the sex difference.

4. The mortality rate among approximately 4,000 women treated during pregnancy was essentially the same as the mortality rate among approximately 9,200 women treated when not pregnant. That the pregnant woman does not represent an increased risk is further borne out by the fact that among a total of 45 fatal reactions to trivalent arsenicals, 25 occurred in women, of whom only 4 were pregnant or post partum.

5. The mortality rate among patients with early syphilis was 1 to 2,800 treated patients. This low death rate is probably attributable to their relative youth and freedom from concomitant disease, rather than to the stage of their syphilis. This interpretation seems most likely since 60 per cent of a total of 45 fatal reactions occurred in patients over 30 years of age, and 50 per cent in patients subjected to the additional strain of concomitant organic disease or toxic factors.

6. Hemorrhagic encephalitis occurred only twice among 27,400 patients given 270,000 injections of trivalent arsenicals in the Syphilis Clinic of the Johns Hopkins Hospital. Only one of these two reactions was fatal. An additional fatality resulted from treatment administered elsewhere. Thus, of the total of 45 fatal reactions, only 2 are attributable to hemorrhagic encephalitis.

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89. Hahn, R. D.: Antisyphilitic Treatment: Mortality Studies; a Clinical, Statistical and Pathologic Analysis of Forty-Seven Fatal Reactions, *Am. J. Syph., Gonorr. & Ven. Dis.* 25:659 (Nov.) 1941.

7. Acute yellow atrophy of the liver was the most frequent cause of death, accounting for nearly 50 per cent of the fatalities. The case incidence was one in 2,300 treated patients; the injection incidence, one in 22,500 trivalent arsenical injections. Acute yellow atrophy occurred 20 times over a seventeen-year period. Fifteen of the 20 patients were women, of whom 4 were pregnant or post partum. Other conditions conducive to liver damage were present in at least 8 additional patients. The hepatic necrosis must, however, be attributed primarily to the arsenicals, perhaps conditioned by a diet deficient especially in the vitamin B-complex.

8. Fatal reactions due to dermatitis or blood dyscrasias were next in order of frequency. The remainder of the deaths, more than one-sixth of the total, were due to a miscellaneous group of immediate, as contrasted with delayed, arsenical reactions. One of these occurred as a result of multiple fat embolism consequent upon an intramuscular injection of bismarsen.

9. Arsphenamine was responsible for 50 per cent of the fatalities. One death, an aplastic anemia, was due to mapharsen. Excessive dosage was a contributing factor in only one patient, a child.

10. Fatal reactions, with the exception of the blood dyscrasias, tend to occur relatively early in the course of treatment, after 10 or less injections.

11. It is estimated that of the entire group of 45 arsenical reactions almost one-half might have been prevented by careful consideration of the patient's general physical condition and appropriate modification of therapy, avoidance of technical errors, and prompt cessation of treatment when signs of major intolerance appeared. By this latter precaution, nearly all deaths due to blood dyscrasias could have been prevented.

12. Autopsy data are presented in 35 cases. The most frequent anatomic findings were hepatic necrosis, dermatitis, and hypoplasia of the bone marrow. Multiple hemorrhages were a frequent finding but occurred always in association with acute yellow atrophy, blood dyscrasias, or fat embolism, conditions in which, irrespective of etiology, such hemorrhages are common.

13. The mortality rate of routine therapy administered to patients of all ages and degrees of debility is less than one-third that of massive dose arsenotherapy administered to a selected group of young adults with early syphilis. The mortality rate for a similarly selected group under routine therapy is less than one-seventh that of massive dose therapy. Further, the case incidence of hemorrhagic encephalitis with massive dose arsenotherapy is sixty to seventy times that of routine therapy.

Levin and Keddle<sup>90</sup> summarize the literature on the toxic effects of mapharsen, noting that although 12,000,000 ampules have been manufactured, only 6 fatalities have been reported. The deaths were reported as due to renal damage in 2 cases, hemorrhagic encephalitis in 1 case, aplastic anemia in 2 cases and acute agranulocytosis in 1 case. About 85 per cent of the patients who have mild or moderate cutaneous reactions to the arsphenamines can tolerate mapharsen, but those who have true exfoliative dermatitis almost always react simi-

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90. Levin, E. A., and Keddle, F.: Toxic Effects Following the Use of Mapharsen: A Review of the Literature Since 1935, *J. A. M. A.* **118**:368 (Jan. 31) 1942.

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9. Arsphenamine was responsible for 50 per cent of the fatalities. One death, an aplastic anemia, was due to mapharsen. Excessive dosage was a contributing factor in only one patient, a child.

10. Fatal reactions, with the exception of the blood dyscrasias, tend to occur relatively early in the course of treatment, after 10 or less injections.

11. It is estimated that of the entire group of 45 arsenical reactions almost one-half might have been prevented by careful consideration of the patient's general physical condition and appropriate modification of therapy, avoidance of technical errors, and prompt cessation of treatment when signs of major intolerance appeared. By this latter precaution, nearly all deaths due to blood dyscrasias could have been prevented.

12. Autopsy data are presented in 35 cases. The most frequent anatomic findings were hepatic necrosis, dermatitis, and hypoplasia of the bone marrow. Multiple hemorrhages were a frequent finding but occurred always in association with acute yellow atrophy, blood dyscrasias, or fat embolism, conditions in which, irrespective of etiology, such hemorrhages are common.

13. The mortality rate of routine therapy administered to patients of all ages and degrees of debility is less than one-third that of massive dose arsenotherapy administered to a selected group of young adults with early syphilis. The mortality rate for a similarly selected group under routine therapy is less than one-seventh that of massive dose therapy. Further, the case incidence of hemorrhagic encephalitis with massive dose arsenotherapy is sixty to seventy times that of routine therapy.

Levin and Keddie<sup>90</sup> summarize the literature on the toxic effects of mapharsen, noting that although 12,000,000 ampules have been manufactured, only 6 fatalities have been reported. The deaths were reported as due to renal damage in 2 cases, hemorrhagic encephalitis in 1 case, aplastic anemia in 2 cases and acute agranulocytosis in 1 case. About 85 per cent of the patients who have mild or moderate cutaneous reactions to the arsphenamines can tolerate mapharsen, but those who have true exfoliative dermatitis almost always react simi-

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90. Levin, E. A., and Keddie, F.: Toxic Effects Following the Use of Mapharsen: A Review of the Literature Since 1935, *J. A. M. A.* **118**:368 (Jan. 31) 1942.

that neoarsphenamine should be used with particular care during times when the meteorologic environment is unusually disturbed, when seasonal effects are more pronounced and during periods of undue cold.

Observations of Nedzel<sup>96</sup> also seem to indicate a seasonal incidence of toxic reactions to neoarsphenamine. In winter neoarsphenamine was somewhat more toxic for rabbits and for white rats in comparison with the same dose given under similar conditions in the autumn. A greater percentage of animals died on days when the temperature was low and the barometric pressure high; also when the temperature was unusually high and the barometric pressure falling abruptly. There was greater damage to the liver among the surviving rabbits in winter than in autumn.

*Untoward Effects of Bismuth Therapy.*—Severe ulcerative stomatitis and nephrosis each have been frequently observed and separately reported as a toxic effect of the use of bismuth in syphilotherapy. The simultaneous occurrence of these complications is reported by Peters<sup>97</sup> in a series of 6 patients observed in the Syphilis Clinic of the Johns Hopkins Hospital. Seeking to explain the cause of these reactions Peters points out the similarity between the pharmacologic and the toxic behavior of bismuth and of lead. As with the latter heavy metal, bismuth may be mobilized and liberated from tissue storage depots during acidosis. In the 5 patients on whom the test was performed, the carbon dioxide-combining power of the blood was found to be lowered. The suggestion is made that bismuth be administered with caution to patients who are prone to acidosis.

Having had twelve months' experience in the tropics under war conditions, Wells and Sewell<sup>98</sup> report that during the hot season patients receiving both neoarsphenamine and a compound containing bismuth are especially prone to albuminuria and microscopic hematuria, without, however, other evidence of impaired renal function. It is believed that with excessive concentration of the urine the excretion of heavy metals by the kidneys may result in a toxic concentration in the convoluted tubules.

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96. Nedzel, A. J.: (a) Daily Variations in the Toxicity of Neoarsphenamine in Rabbits, *J. Lab. & Clin. Med.* **27**:715 (March) 1942; (b) Daily Variations in the Toxicity of Neoarsphenamine in White Rats, *ibid.* **27**:719 (March) 1942; (c) Seasonal Injuries of Liver and Kidneys Due to Neoarsphenamine, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:209 (March) 1942.

97. Peters, E. E.: Bismuth Stomatitis and Albuminuria, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:84 (Jan.) 1942.

98. Wells, H. G., and Sewell, S. A.: Albuminuria in the Treatment of Syphilis in the Tropics, *J. Roy. Nav. M. Serv.* **4**:389 (Oct.) 1941.

## EARLY SYPHILIS

*Infectious Relapse.*—Stressing the public health aspects of infectious relapse in syphilis and the difficulties in detecting the lesions of relapse, Kern<sup>99</sup> discusses 80 cases from the files of the Vanderbilt University Hospital Clinic, concluding:

1. Relapse occurs most frequently in patients whose treatment is begun in the primary stage of infection, slightly less frequently when treatment is begun in the secondary stage, and extremely infrequently when it is begun in the latent stage.
2. Two-thirds of the patients developing mucocutaneous relapse have lesions at sites which are particularly favorable for transmission of infection.
3. Relapse is characterized by paucity of lesions. The latter are usually papular or annular in type.
4. Serologic tests for syphilis are positive in practically 100 per cent of relapse cases.
5. Eighty per cent of recurrent lesions (relapse) develop in the first two years of infection if treatment is suboptimal. If optimal treatment is given, relapse may be delayed beyond the usual time. Two-thirds of the cases of relapse occur within one year after treatment ceases.
6. As a rule, the frequency of relapse decreases as the number of arsenical injections increases. . . .
7. The accepted standard of adequate treatment will not prevent infectious relapse in all cases.

*Osseous Lesions.*—Reynolds and Wasserman<sup>100</sup> have been able to find in the available literature 15 cases of destructive bone lesions associated with early syphilis and report 15 of their own cases of a similar condition. Their cases were encountered among some 10,000 instances of early syphilis observed in the Syphilis Division of the Medical Clinic and the wards of the Johns Hopkins Hospital from 1919 to 1940. Included are examples of osteitis, osteomyelitis and osteoperiostitis.

The bones of the skull are most frequently affected; the frontal, the parietal and the nasopalatine bones are especially vulnerable. The sternoclavicular region ranks next. The long bones are not as commonly involved.

The cardinal symptoms of destructive bone lesions are pain and localized tumefaction. The pain varies markedly in intensity, its severity being dependent on the degree of associated periostitis, and is usually worse at night. Lesions were at times completely asymptomatic and were discovered only when the finding of one lesion prompted a roentgen study of other portions of the skeleton.

99. Kern, J. C.: Infectious Relapse in Syphilis, *Northwest Med.* **40**:328 (Sept.) 1941.

100. Reynolds, F. W., and Wassermann, H.: Destructive Osseous Lesions in Early Syphilis, *Arch. Int. Med.* **69**:263 (Feb.) 1942.



The onset of symptoms may precede or follow the secondary eruption. There is no correlation between the type of secondary eruption and the presence of bone lesions. The most frequently associated condition is arthritis, which usually involves several joints. Occasionally, the patient is ill with fever, anemia, weakness, loss of weight and other evidences of toxemia.

In the authors' series the patients in all but 2 of the 15 cases responded favorably to routine antisyphilitic treatment. These 2 patients, with treatment-resistant precocious malignant tertiarism, did respond to malaria therapy.

The lesions in the skull are characteristic, consisting of irregularly circular areas of decreased density having a moth-eaten appearance. Elsewhere, the bony changes are less diagnostic, although involvement about the sternoclavicular joint is suggestive. The thinner and more porous bones of the skull are the ones commonly affected, and it was noted that lesions posterior to the lambdoidal suture are rare. Soft tissue swelling or wavy periosteal markings parallel to the surface of the bone are indicative of concomitant periostitis.

*Gastric Lesions.*—Reynolds<sup>101</sup> has reviewed the literature pertaining to the gastric lesions of early syphilis. Patients with early syphilis not infrequently have complaints referable to the gastrointestinal tract, and several observers have noted hypochlorhydria. A limited number of gastroscopic and postmortem studies are available. Histopathologic reports must be interpreted with considerable reserve because of rapid postmortem autolysis. In summary, the author concludes that two types of gastric lesion may be associated with early syphilis: (1) a superficial gastritis, a not uncommon lesion of little clinical significance, most readily demonstrated by gastroscopic examination, and (2) an interstitial infiltration of the submucosa and the muscularis of the stomach, with thickening of the wall, and stenosis of the lumen, a rare example of "precocious tertiarism."

*Uveitis.*—Because the significance attributed to the various systemic infections and diseases believed to cause endogenous uveitis varies enormously in different clinics, in different localities and in succeeding decades, Guyton and Woods<sup>102</sup> have analyzed 562 cases, all of which have been thoroughly studied. In all cases the patients were admitted to the wards of the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital between Nov. 1, 1925 and July 1, 1939. No patients

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101. Reynolds, F. W.: Gastric Lesions Associated with Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:218 (March) 1942.

102. Guyton, J. S., and Woods, A. C.: Etiology of Uveitis: A Clinical Study of Five Hundred and Sixty-Two Cases, *Arch. Ophth.* **26**:983 (Dec.) 1941.

examined in the outpatient departments or in private offices of the institute were included in this study.

The authors divided their cases into two groups. The first consisted of 244 cases in which the sum total of available evidence pointed clearly to some definite etiologic factor. The second and larger group consisted of the remaining 318 cases in which the evidence was considered either too scanty or too inconclusive to permit more than a tentative diagnosis of the cause of the uveitis.

They found the most common cause of uveitis to be tuberculosis, 49.7 per cent of the entire group; syphilis was responsible in 10.5 per cent and gonorrhea in 4.6 per cent. Other diseases causing uveitis are recorded in tabular form for both groups of cases.

#### FEVER THERAPY OF EARLY SYPHILIS<sup>103</sup>

Boak and her co-workers<sup>103</sup> report a study of the effect of a single prolonged period of artificial fever (nine to fifteen hours at 41.0 to 41.5 C.) on 8 patients with primary and with secondary syphilis. Artificial fever of this magnitude, administered by the radiant energy method, resulted in prompt resolution of the early lesions in all cases, but mucocutaneous relapse developed within four months in 4 of the 5 patients who subsequently received no chemotherapy. The fifth patient continued to have a positive serologic reaction for syphilis but had no obvious infectious relapse.

Experimentally in rabbits Boak, Carpenter and Warren<sup>104</sup> have found that syphilis can be cured by a mode of therapy combining a subcurative dose of neoarsphenamine (10 mg. per kilogram of body weight) with subcurative artificial fever (three or four hours at 41.5 C.). When the drug was given immediately before a fever treatment, 100 per cent of the animals were cured, but when it was given at the termination of the fever, only 75 per cent recovered. The authors attribute the higher percentage of cures obtained when the neoarsphenamine was given before the fever either to a more widespread distribution of the drug resulting from an increased vascular response or to an increase in its spirocheticidal action as a result of the elevation in body temperature.

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103. Boak, R. A.; Carpenter, C. M.; Jones, N.; Kampmeier, R. H.; McCann, W. S.; Warren, S. L., and Williams, J. R., Jr.: The Inadequacy of a Single Prolonged Fever for the Treatment of Early Acute Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:291 (May) 1942.

104. Boak, R. A.; Carpenter, C. M., and Warren, S. L.: The Concurrent Treatment with Fever and Neoarsphenamine of Experimental Syphilis in Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:282 (May) 1942.

# Summary of Recent Reports on Massive Dose Arsenotherapy

Author	No. of Patients			Treatment			No. of "Failures," Including Possible Reinfections	No. of Reactions						Comment		
	Number of Patients Treated	Returning for Re-treatment	No.	Method of Administration	Total Dose, Mg.	Duration of Treatment, Days		Death	Toxic effects	Peripheral Neuritis	Fever		Exfoliative Dermatitis			
											Arsenical Administered	Phenamine			Pri-mary	Sec-on-dary
Lefler, Chargin and Hyman <sup>10a</sup>	111	—	Neoarsphenamine	Intra-venous drip	4,000	5	6	1	2	50	39	69	71	1	4	Most of unsatisfactory results in patients receiving smaller amounts of mapharsen
	157	4	Mapharsen	Intra-venous drip	400 to 1,100	5	24	0	3	35	5	119	39	0	2	
	118				1,200		8									
Elliott, Baehr, Shaffer, Usher and Lough <sup>10b</sup>	1,000 (908 studied in detail)	—	Mapharsen	Intra-venous drip and multiple injections	250 to 1,250	5	5	5	—	"11%"	—	"48%"	"41%"	0	2	A cooperative progress report from 13 hospital clinics
Ratner <sup>10c</sup>	180	—	Mapharsen	Intra-venous drip	1,200	5	8	0	2	—	—	—	—	0	0	
Spiller <sup>10d</sup>	70	—	Mapharsen	Intra-venous drip	—	5	—	1	—	—	"No other serious reactions"			—		
Goldblatt <sup>10e</sup>	100	—	Mapharsen	Daily injections	1,200	12	—	0	—	—	"No serious reactions"			—	Anemia frequent	
Schoch <sup>10f</sup>	70	—	Mapharsen	Multiple injections	1,200	10	10% failures, 10% "pending"	0	1	—	—	—	—	—	1	1 case of purpura
Barletta <sup>10g</sup>	10	0	Arsenosan *	Intra-venous drip	1,200 to 1,600	5	0	0	—	—	"No serious reactions"			—		
Bowman and Sheehan <sup>10h</sup>	141	8	Mapharsen	Intra-venous drip	1,200	5	8	0	1	5	—	—	68	—	—	4 pregnant women treated



*Combined Therapy with Fever and Arsenicals.*—A résumé of fever therapy in the management of syphilis is given by Phillips.<sup>105</sup> In addition to its proved value in neurosyphilis, the author believes that "the combination of chemo-fever therapy is by far the shortest and surest method known in curing early syphilis." Sixty-two patients with early syphilis have been treated by the author in this manner. However, many had received chemotherapy previously, a fact making analysis of the data difficult. Four relapses are recorded, and 23 patients remain seropositive, which does not support the contention that his method is the "surest method known." No data as to toxic reactions are given.

Coutts and his associates<sup>106</sup> have made a preliminary report on the immediate results of treatment of 5 patients with early syphilis by the Simpson technic of one day therapy with combined fever and massive doses of an arsenical. The patients were given ten hours' fever therapy at 41.1 C. Simultaneously, oxarsolan (0.24 Gm.) was administered by intravenous drip. Twelve hours before the combined arsenofever therapy the patients received 0.2 Gm. of an insoluble compound containing bismuth. The treatment was well tolerated by all 5 patients, and infectious lesions promptly failed to yield material positive for *S. pallida* on dark field examination. The patients have not been followed sufficiently long to allow any assessment of the ultimate outcome.

With his usual uncritical judgment, hyperenthusiasm and willingness prematurely to capitalize journalistically on sober scientific experimentation, de Kruif<sup>107</sup> has unhappily drawn nationwide attention to this "one day cure" for syphilis. This tendency of medical journalists to raise false hopes in lay minds can only be deplored. With all due respect to democratic freedom of speech, it is too bad that no censorship exists to compel conservative accuracy from sensational writers on medical subjects.

#### INTENSIVE ARSENOTHERAPY

*Clinical Results.*—Massive dose arsenotherapy is being used more and more extensively, not only in this country but in Canada and in South America. Accurately to discuss each report of this method of therapy would involve needless repetition. In the table we have

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105. Phillips, K.: *Résumé of Fever Therapy in Management of Syphilis*, J. Arkansas M. Soc. **38**:139 (Dec.) 1941.

106. Coutts, W. E.; Figueroa, M.; Bustamante, B.; Valenzuela, E., and Coutts, J.: *Tratamiento de la sífilis reciente en un día por el método combinado y simultáneo bismuto-arsenical-piretotermino*: Comunicación preliminar, Rev. chilena de hig. y med. prev. **4**:229 (Dec.) 1941.

107. de Kruif, P.: *Found: A One-Day Cure for Syphilis*, Read. Digest **41**:10 (Sept.) 1942.

attempted, insofar as possible, to summarize the work of numerous investigators<sup>108</sup> who have been concerned with massive dose arsenotherapy.

*Intensive Arsenotherapy of Latent and of Late Syphilis.*—Demonstration of the fact that early syphilis can be cured by massive dose arsenotherapy has led Kaplan<sup>108a</sup> to employ the method in the treatment of patients with latent syphilis and in the late stages of the disease. At Sing Sing Prison 192 patients with syphilis were treated by the intravenous drip method of intensive arsenotherapy, with or without fever therapy. Since approximately 350 men are admitted to the Sing Sing syphilis clinic yearly and most of them remain incarcerated for no less than two years, it was felt that this was an excellent opportunity to follow results of intensive treatment of late and of latent syphilitic infection.

The arsenical employed in the treatment of all patients was mapharsen. Between 150 and 400 mg. of the drug was added to solution of sodium chloride, dextrose or sodium lactate; when massive

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108. (a) Leifer, W.; Chargin, L., and Hyman, H. T.: Massive Dose Arsenotherapy by Intravenous Drip Method, *J. A. M. A.* **117**:1154 (Oct. 4) 1941. (b) Elliott, D. C.; Baehr, G.; Shaffer, L. W.; Usher, G. S., and Lough, S. A.: An Evaluation of the Massive Dose Therapy of Early Syphilis, *ibid.* **117**:1160 (Oct. 4) 1941. (c) Rattner, H., in discussion on Elliott and others.<sup>108b</sup> (d) Spiller, W. F., in discussion on Elliott and others.<sup>108b</sup> (e) Goldblatt, S., in discussion on Elliott and others.<sup>108b</sup> (f) Schoch, A. G., in discussion on Elliott and others.<sup>108b</sup> (g) Barletta, J. L.: Tratamineto de la sífilis por el método Norteamericano de los cinco días o arsenoterapia intensiva, *Día méd.* **13**:1193 (Nov. 10) 1941. (h) Bowman, G. W., and Sheehan, F. G.: Massive Arsenotherapy in Syphilis, *J. Indiana M. A.* **34**:665 (Dec.) 1941. (i) Scholtz, J. R.: Intensive Arsenotherapy of Syphilis, *Venereal Disease Bulletin* 1, State of California Department of Public Health, 1941, no. 7, p. 3. (j) Prats, G. F.; Infante Varas, L.; Simon, K. T., and Harazsti, E.: Tratamiento masivo "gota a gota" de la sífilis, *Rev. argent. dermatosif.* **26**:65, 1942. (k) Body, E. F.; Harazsti, E., and Giacamon, J.: Experiencia en los servicios de lucha antivenerea empleando arsenobenzoles y arsenoxides, *ibid.* **26**:92, 1942. (l) Sadusk, J. F., Jr.; Craige, B., Jr.; Brookens, N.; Poole, A. K., and Strauss, M. J.: Observations on the Massive Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method: I. Toxicology, Clinical Observations and Therapeutic Results, *Yale J. Biol. & Med.* **14**:333 (March) 1942. (m) Berry, N. E.: The Treatment of Early Syphilis by the Massive Dose Method, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:204 (March) 1942. (n) Usher, B., and Hill, A. E.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, *Canad. M. A. J.* **46**:342 (April) 1942. (o) Brun, J. F.; Ramirez, D., and Román, A.: Segundo informe para el boletín de salubridad e higiene del departamento de salubridad sobre la arsenoterapia masiva, *Rev. méd. veracruzana* **22**:3691 (May) 1942. (p) Prunes, L., and Hevia, P. H.: Massive Arsenotherapy in Early Syphilis: Report of Sixty Cases in Which Neoarsphenamine Was Given, *Arch. Dermat. & Syph.* **45**:894 (May) 1942. (q) Kaplan, B. I.: Intravenous Drip Method in Intensive Arsenotherapy of Syphilis with Particular Reference to Its Application for Latent Syphilis and for Late Stages of the Disease, *ibid.* **45**:941 (May) 1942.

dose arsenotherapy alone was employed, the drug was given in five consecutive daily infusions. All patients were men between the ages of 18 and 63. There were 126 Negroes, 65 white persons and 1 Chinese. Of the entire group of 192 patients, 117 were treated by the intravenous drip method just described. When this method was combined with artificial fever therapy, fever was usually produced by intravenous injection of typhoid vaccine, and the injections of vaccine were so administered that two or three days of massive dose arsenotherapy was immediately followed by fever therapy.

No serious toxic reaction or fatality was observed in the group. Minor reactions, such as fever, peripheral neuritis, toxicoderma and gastrointestinal symptoms were common.

The present paper is considered as a preliminary report, since the study was started in November 1939 and completed in July 1941. The author states that the results to date look encouraging. However, adequate time has not passed to permit one to evaluate the results of this form of treatment.

*Intensive Arsenotherapy in Infants and Children.*—Applying intensive arsenotherapy to the treatment of congenital and acquired syphilis in infants and children, Levin, Hoffman and Koransky<sup>109</sup> have studied three groups of patients: (1) 14 infants under 6 months of age with manifest congenital syphilis; (2) 13 infants and young children between the ages of 6 months and 6 years, and (3) 4 children with early acquired syphilis. From 1.6 to 3.0 mg. of mapharsen per pound (0.45 Kg.) of body weight was given, with no significant toxic reactions. In 8 of the 31 patients reversal of the serologic reaction for syphilis occurred, and in 2 others the trend of the reagin titer is favorable. Two have been retreated because of rising reagin titers.

*Electrocardiographic Abnormalities Associated with Massive Dose Arsenotherapy.*—Geiger and his co-workers<sup>110</sup> observed significant electrocardiographic abnormalities during or shortly after massive dose arsenotherapy in 21 of 23 patients. The principal changes were concordant diminution of the amplitude of the T waves in all leads and frequently inversion of the T wave in leads other than the third. In every case the altered electrocardiographic features returned to the pretreatment control condition within a few weeks, and the authors

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109. Levin, I. M.; Hoffman, S. J., and Koransky, D.: Massive Dose Intravenous Arsenotherapy of Congenital and Acquired Syphilis in Infants and in Children, *Am. J. Dis. Child.* **63**:201 (Jan.) 1942.

110. Geiger, A. J.; Craige, B., Jr., and Sadusk, J. F., Jr.: Electrocardiographic Abnormalities Associated with Massive Arsenotherapy, *Yale J. Biol. & Med.* **14**: 357 (March) 1942.

believe the abnormalities to represent toxic effects of a transient and benign nature due to arsenic.

*Quantitative Serologic Tests to Evaluate Results of Massive Dose Arsenotherapy.*—Dussert<sup>111</sup> indicates the utility of quantitative serologic tests in evaluating the results of massive dose arsenotherapy. In his series the reversal of the serologic reaction for syphilis occurred more gradually when the reagin titer at the beginning of treatment was high than when the initial titer was low. The author believes that patients treated with massive dose arsenotherapy should be followed with serial titered serologic tests before treatment is considered a failure because of seroresistance.

*Experimental Work on Massive Dose Arsenotherapy.*—Eagle and Hogan<sup>112</sup> state that the observation that early syphilis may be effectively treated, and in most cases definitely cured, within five days by administering neoarsphenamine or mapharsen by intravenous drip is of obvious importance to the individual patient and to the current control program. The intensive procedure, however, is many times more dangerous than standard methods of treatment. Whether this increased risk is justified by the somewhat more rapid control of infectiousness and by the perhaps more favorable early results achieved by this method is debatable. It is clear that the traditional schedule of weekly injections for eighteen months is wholly arbitrary. The authors state:

Given as three variables, (a) the total duration of treatment, (b) the number of injections and (c) the size of the individual dose, there are obviously an infinite number of possible combinations. Given further the fact that a 5-day and an 18-month schedule may be of comparable therapeutic efficacy, it should be possible, with the same drugs, to find effective methods of treatment which combine the speed of one and the safety of the other to an optimum degree.

Because of the very number of possible combinations of time and dose and because of the difficulties inherent in any clinical evaluation, the initial problem of orientation seemed clearly one for the laboratory rather than the clinic.

The authors attempted in the fall of 1939 to determine in syphilitic rabbits the toxicity and the therapeutic activity of twelve different treatment schedules:

Intravenous drip (5 and 6 hours daily) for 1, 2 and 4 days.

Multiple injections each day for 1, 2 and 4 days.

Single daily injections for 1, 4 and 12 days.

Injections every other day (3 times weekly) for 4 and 8 weeks.

Weekly injections for 6 weeks.

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111. Dussert, E.: Utilidad de los métodos cuantitativos como criterio para valorar el efecto de un tratamiento en la lúes, *Rev. méd. de Chile* **69**:743 (Nov.) 1941.

112. Eagle, H., and Hogan, R. B.: The Intravenous Drip and Other Intensive Methods for the Treatment of Early Syphilis, *Science* **95**:360 (April 3) 1942.



Although this is a preliminary report, and the work has not yet been completed, 2,000 animals have been used to date. The results seem sufficiently clear to justify the following generalizations, which are presented at this time because of their implications with respect to the present day treatment of early syphilis:

Within broad limits, the curative dose of Mapharsen with any one type of treatment was largely independent of the time period over which that treatment was given. Indeed, in seven schedules involving rapid intravenous injections, in which the total duration of treatment varied from 10 seconds to 6 weeks, the interval between injections from 2 hours to 1 week, and the total number of injections from 1 to 16, the minimal curative dose varied only between 4 and 8 mg per kg. Although there was some suggestion that repeated doses at short intervals were more effective than either one large dose, or repeated doses at weekly intervals, the data are as yet inconclusive.

The minimal curative dose of the intravenous drip procedure, whether for one day or for four days, varied only between 7 to 12 mg per kg. It is of interest to note that Mapharsen administered by intravenous drip has been consistently less effective than Mapharsen administered by repeated injections over the same time period.

Of primary importance is the fact that, on every treatment schedule yet tried, the total amount of arsenical which could be administered without killing the animal increased directly with the total duration of treatment. Of secondary importance is the fact that, within a fixed time period, somewhat larger amounts of arsenical could be administered by increasing the frequency of injections. Thus, on daily injections for 4 days, the maximal tolerated dose was 30 mg. per kg. This was increased to 40 mg per kg by giving 4 injections daily over the same time period, and to 48 mg per kg by giving a continuous intravenous drip for six hours daily on each of four consecutive days.

It is shown that mapharsen given by intravenous drip is apparently less effective than the same amount of arsenical given by repeated single intravenous injections. More important still is the fact that the tolerated dose of arsenical given by simple injection can apparently be increased almost without limit merely by prolonging the duration of treatment. The authors state:

Since the total curative dose of Mapharsen in rabbits is, within broad limits, approximately constant, and since the total tolerated dose on any schedule of injections increases directly with the duration of treatment, it necessarily follows that *the margin of safety between the toxic and therapeutic dose ("chemotherapeutic index") may be increased continuously by prolonging the duration of treatment.* Conversely, on any schedule of injections, the shorter the total time period over which the treatment is administered, the lower is the margin of safety afforded. [The italics are those of Eagle and Hogan.]

Thus, (1) on six weekly injections the total tolerated dose (60 mg per kg) was 7.5 times the minimal curative dose (8 mg per kg), as compared with a margin of 1.4 for a single injection. Moreover, the margin of safety afforded by 30 weekly injections would probably be not far from 30. (2) When the injections were given three times weekly for four weeks, the chemotherapeutic index was 12; and it is estimated that the index on a similar eight-week schedule would be about 24. (3) With four consecutive daily injections, the margin of safety

was approximately 6; and it is estimated that 12 daily injections will provide a margin of approximately 10. (4) Multiple daily injections over a four-day period gave a safety factor of approximately 10; and an intravenous drip for the same period provided a margin of safety of only 4. In both cases, a shorter time period (1 or 2 days' treatment) gave an even longer chemotherapeutic index; while a longer treatment period would presumably have resulted in a correspondingly wider margin of safety.

In the absence of evidence to the contrary, we must assume that these same considerations apply in human beings. Indeed, such data as are available from the clinic are in accord with the dual thesis that the total curative dose of Mapharsen varies only slightly with the frequency and total duration of treatment, while the total tolerated dose varies directly with the time period over which the arsenical is administered. . . .

On the basis of our animal results to date, those requirements [for an effective and safe treatment schedule] would be at least approximated in the treatment of humans by (a), injections of 20 mg Mapharsen (0.3 mg per kg) repeated twice daily for 4 to 8 weeks; (b), daily injections of 30 mg Mapharsen (0.5 mg per kg), continued for 5 to 10 weeks; or (c), injections of 60 mg Mapharsen (1 mg per kg) repeated three times weekly for 5 to 10 weeks. . . .

For purposes of orientation, a clinical study has been organized in twelve cooperating clinics, in which the following three schedules are being used for the treatment of early syphilis: (a) Injections 3 times weekly for 4 weeks. (b) Injections 3 times weekly for 6 weeks. (c) Injections 3 times weekly for 8 weeks. On the last two schedules, some of the patients are being given concomitant weekly injections of bismuth. The results to date with respect to toxicity are encouraging. Further modification may, however, prove desirable in the light of continuing clinical experience, and particularly, in the light of end-results.

Continuing their studies on the toxicity of mapharsen given in massive doses, Magnuson and Raulston<sup>113</sup> report that the maximum tolerated dose of mapharsen given to anesthetized dogs in three daily doses for each of five successive days was 10 mg. per kilogram of body weight per day and that the minimum lethal dose administered under the same conditions was 14 mg. per kilogram per day. These findings indicate that the maximum tolerated dose and the minimum lethal dose of mapharsen given in interrupted doses do not differ significantly from such doses of the drug when it is given by continuous intravenous drip, the conditions of administration otherwise being equal. Blood levels of arsenic were similar in the two instances, although there was a somewhat longer retention of arsenic in the tissues of animals treated with interrupted doses.

Kolmer and Rule<sup>114</sup> have compared the effectiveness of neoarsphenamine and of mapharsen administered by the continuous intravenous drip method once a day for five successive days with that of

113. Magnuson, H. J., and Raulston, B. O.: Toxic Dose of Mapharsen Given in Interrupted Doses, *Ven. Dis. Inform.* **22**:431 (Dec.) 1941.

114. Kolmer, J. A., and Rule, A. M.: Massive Arsenotherapy by the Continuous Intravenous Drip Method: Treatment of Acute Syphilis in Rabbits, *Arch. Dermat. & Syph.* **44**:1055 (Dec.) 1941.

the same drugs administered in single doses by intravenous injection with a syringe in the treatment of acute syphilitic orchitis in rabbits. The minimal curative doses of both compounds by the two methods of administration were practically the same, being about 0.02 Gm. of neoarsphenamine and 0.005 Gm. of mapharsen per kilogram of body weight. Single doses of either compound administered by the syringe method appeared to have a more prompt effect on the spirochetes in the testicular lesions than a comparable total dose administered by the drip method.

*Intensive Syphilotherapy with Both an Arsenical and a Compound Containing Bismuth.*—By using combinations of fractions of the minimum curative dose of various arsenicals (mapharsen and neoarsphenamine) with fractions of the minimum curative dose of various preparations containing bismuth (bismuth sodium tartrate, thio-bismol and bismuth ethyl camphorate), Clausen, Longley and Tatum<sup>115</sup> have determined the quantitative nature of the combined action of these two types of compounds in experimental rabbit syphilis. Their data indicate the therapeutic efficiency of the combination to be one of simple addition rather than potentiation or inhibition, whereas the cototoxicity was found to be less than additive. There was, in effect, a greater margin of safety when a compound containing bismuth and an arsenical were administered concurrently than when either was used alone in correspondingly effective doses. The combination of mapharsen with a slowly absorbed preparation containing bismuth gave the widest margin of safety.

Unfortunately, as a criterion of "cure," lymph node transfers were made three weeks after the last treatment, a time interval too short in which to observe a condition analogous to infectious relapse. After subcurative doses of arsenical drugs node transfers may be, and frequently are, negative at three weeks and positive at six months.

On the basis of their experiments, the authors propose a modification of intensive arsenotherapy to include the concurrent administration of a compound containing bismuth, with the expectation of reducing the hazards of massive dose therapy.

#### LATE SYPHILIS

*Syphilis and Gastrointestinal Disorders.*—Levy and Winkelstein<sup>116</sup> review the controversial literature pertaining to syphilis of the alimentary canal. In their opinion, esophageal syphilis may be in the form

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115. Clausen, N. M.; Longley, B. J., and Tatum, A. L.: The Quantitative Nature of the Coaction of Bismuth and Arsenical Compounds in the Therapy of Experimental Syphilis, *J. Pharmacol. & Exper. Therap.* **74**:324 (March) 1942.

116. Levy, M. H., and Winkelstein, A.: Syphilis of the Alimentary Canal (Excluding the Stomach), *Urol. & Cutan. Rev.* **46**:221 (April) 1942.

of direct extensions of the syphilitic process from contiguous tissues or of gummas; involvement of the small intestine is suggested when enteritis or stricture complicates early or late stages of the disease, and primary, secondary and tertiary lesions of the rectum and colon are recognizable.

Goldsmith<sup>117</sup> has reviewed the literature pertaining to the prevalence, pathology, diagnosis and treatment of syphilis of the stomach, reporting a case which was unusual in that there was extensive involvement of the cardia.

A study of the gastroscopic findings in 12 patients having untreated syphilis of the stomach has been made by Patterson, Rouse and Bagwell.<sup>118</sup> The most common symptoms referable to the stomach in this group of patients were burning epigastric pain, with or without relief after the ingestion of food; nausea; vomiting; cachexia; hematemesis, and a palpable mass. All patients had positive serologic reactions for syphilis and absence of free hydrochloric acid in the stomach. With 1 exception there was roentgen evidence of a filling defect, ulceration, tumefaction, prepyloric narrowing or diffuse thickening of the stomach.

The lesions as seen through the gastroscope in all instances associated with latent syphilis were of three morphologic types: (1) single or multiple ulcerations of the gastric mucosa; (2) nonulcerative tumors of the stomach, and (3) flattened or thickened appearance of the rugae evidencing local or diffuse, subacute or chronic infiltration of the stomach. Roentgenograms of all three types of lesions are included in the article. The authors state that the characteristic type of syphilitic ulcer seen in the lower third of the stomach resembles closely the gummatous syphilitic ulcerations seen on the palate. It has a smooth, shallow base, sloping edges, and purplish red serpiginous borders. At times it is difficult to differentiate the round syphilitic ulcer of the stomach from peptic ulcer. The purplish red sloping edges with a dirty gray base are more characteristic of a syphilitic ulcer. It is more difficult to differentiate infiltrating lesions of syphilis which produce tumors of the stomach from similar lesions of other origin. They believe that the prominence of superficial blood vessels on the borders of the tumor and pallor of the mucosa due to fibrosis or to mucosal atrophy from pressure from beneath are differential points.

*Syphilis and Gynecologic Disorders.*—Falk and Kempner<sup>119</sup> discuss the effect of latent syphilis on wound healing in a series of 930 con-

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117. Goldsmith, G. A.: The Diagnosis and Treatment of Gastric Syphilis, New Orleans M. & S. J. **94**:284 (Dec.) 1941.

118. Patterson, C. O.; Rouse, M. O., and Bagwell, J. S.: The Gastroscopic Diagnosis of Syphilis of the Stomach, South. M. J. **35**:565 (June) 1942.

119. Falk, H. C., and Kempner, I.: Healing of Operative Wounds in Syphilitic Women, Am. J. Surg. **54**:674 (Dec.) 1941.

secutive laparotomies that fitted certain criteria which were performed on patients admitted to the gynecologic service of the Harlem Hospital, New York. Of 450 patients with positive Kahn reactions, wound infections occurred in 16.4 per cent, whereas in a group of 480 patients with negative Kahn reactions, there was a 12.9 per cent incidence of wound infections.

*Syphilis and Orthopedic Conditions.*—Comroe<sup>120</sup> outlines a classification of syphilitic joint disease as follows: (1) in congenital syphilis: Parrot's syphilitic osteochondritis, symmetric serous synovitis and uncommon forms, including gummatous synovitis, syphilitic dactylitis and suppurative joint disease; (2) in the secondary stage: arthralgia, synovitis, hydrarthrosis, tenosynovitis, bursitis, arthritis resembling rheumatic fever and rheumatoid arthritis, and (3) in tertiary syphilis: gummatous arthritis, Charcot's joint, chronic syphilitic arthritis, juxta-articular gumma and juxta-articular node.

Comroe notes that the presence of syphilis should be suspected in any case of bilateral painless hydrops of the knees in children, in any involvement of a joint simulating rheumatic fever which does not respond promptly to adequate salicylate therapy and in any deforming arthritis limited to a single joint.

*Syphilis and Ophthalmic Conditions.*—A comprehensive review of fifteen years' experience with syphilis as encountered in a large hospital for patients with disorders of the eye is analyzed by Assinder.<sup>121</sup> Of 1,015 patients with positive and doubtful serologic reactions for syphilis, there were 19 with gummas in orbital areas, 17 with scleritis, 553 with keratitis, 96 with iritis, 87 with choroidoretinitis, 74 with optic atrophy, 19 with optic neuritis, 119 with palsy of a nerve and 31 with miscellaneous disorders. In all cases the keratitis was of the diffuse interstitial type, and in 97 per cent it was congenital. In only 15 of the 96 instances of iritis was the condition associated with early syphilis.

#### CARDIOVASCULAR SYPHILIS

*Diagnosis of Uncomplicated Syphilitic Aortitis.*—Uncomplicated syphilitic aortitis remains one of the most difficult lesions to detect clinically. The symptomatology may be insignificant; physical signs may be indefinite and concomitant diseases not infrequently complicate the clinical picture. An annotator<sup>122</sup> in the *Lancet* points out that the use of electrocardiographic and of roentgen examination in the early diagnosis of syphilitic aortitis is also limited. Electrocardiograms seldom

120. Comroe, B. I.: Syphilitic Joint Disease, *Urol. & Cutan. Rev.* **46**:234 (April) 1942.

121. Assinder, E. W.: Syphilis in Ophthalmology (Middlemore Lecture), *Brit. J. Ophth.* **26**:1 (Jan.) 1942.

122. Early Diagnosis of Syphilitic Aortitis, *Lancet* **1**:360 (March 21) 1942.

show evidence of the condition, unless there is involvement of the coronary ostiums or the aortic valve becomes incompetent. The main obstacle in detecting the condition either by a teleroentgenogram or by fluoroscopic examination is the difficulty of obtaining a standard of normal measurement for the size of the aorta. Fluoroscopic examination may reveal increased pulsations, local dilatation, increased density of the aortic wall or irregularity of its outline. None of these changes, however, is pathognomonic.

Boharas and his collaborators<sup>123</sup> have analyzed from the standpoint of roentgen studies and physical examination, 200 syphilitic patients without saccular aneurysm, arterial hypertension or vascular disease and 200 nonsyphilitic control patients of the same age and sex distribution. The diagnosis of syphilis was based on the presence of confirmed positive serologic reactions. In the control group syphilis was excluded by history and physical examination, as well as confirmed negative serologic reactions. In each patient the aorta was measured by the Vaquez-Bordet, the Hampton and the Fray technic. As to the Vaquez-Bordet measurements of the 200 nonsyphilitic and the 200 syphilitic patients the authors say:

The impressive feature of this comparison is that, with a few exceptions, the two groups present identical measurements. The increase in the size of the aorta is virtually the same with advancing years in syphilitic and non-syphilitic patients and is apparently due to arteriosclerosis.

They stress that before the diagnosis of diffuse aortic dilatation can be made in the posteroanterior view, this must be supplemented by an oblique view in order to exclude tortuosity of the aorta.

The Hampton measurement also failed to distinguish the syphilitic from the nonsyphilitic aorta prior to the onset of marked aortic dilatation, and with few exceptions the two groups presented similar measurements. It was found that in 7.5 per cent of the normal subjects and in 14 per cent of the syphilitic patients the aortic root measured between 6.2 and 7.4 cm. The authors believe that the increased incidence among syphilitic patients is no doubt significant but state that it is impossible to evaluate this fact clinically.

They had no more success in diagnosing syphilitic aortitis with the Fray measurement. In the corresponding age groups there was little difference between the nonsyphilitic and the syphilitic patients with regard to the indexes obtained.

The authors do not believe that local dilatation with increased pulsation or increased density and irregularity of the aortic wall, as observed during fluoroscopy, is pathognomonic of syphilitic aortitis.

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123. Boharas, S.; Hollander, L., and Goldsmith, M.: The Early Diagnosis of Syphilitic Aortitis, *Am. J. M. Sc.* 203:54 (Jan.) 1942.

The least reliable of all physical signs was a visible pulsation in the suprasternal notch. Increased retromanubrial dullness was found to be present in many patients of the nonsyphilitic group, with and without arterial hypertension. A slight systolic aortic murmur was noted in 1.5 per cent of the syphilitic patients and in 2 per cent of the normal control group. A tympanitic second aortic sound was of more value than other physical signs, since it occurred in 2.5 per cent of the syphilitic patients but only once in 500 normal patients of the same age group. Because the sign is rare in normal persons, the authors express the belief that it is of diagnostic value providing arteriosclerosis, valvular heart disease and hypertension are ruled out.

The electrocardiograms of 160 syphilitic patients were analyzed. The interval between the appearance of a chancre and the electrocardiographic study varied from three to thirty-nine years, with an average of fourteen and seven-tenths years. Only 5 of these patients presented abnormal tracings. As a rule, electrocardiographic changes occur late in the course of cardiovascular syphilis and are generally due either to aortic regurgitation or to stenosis of the coronary orifices. A normal electrocardiogram does not rule out cardiovascular syphilis, since in 1 patient with aortic regurgitation, 3 patients with saccular aneurysm and 3 patients with diffuse aortic dilatation, no abnormalities were noted in the electrocardiographic tracings.

The authors conclude:

This study supports the contention that a positive clinical diagnosis of early syphilitic aortitis is practically impossible. This study clearly shows that a reliable diagnosis cannot be made before wide dilatation of the aorta has occurred. We agree . . . that a positive diagnosis of cardiovascular syphilis can be made only when one or more of the following findings is present: 1, a saccular aneurysm of the aorta or innominate artery; 2, aortic regurgitation appearing for the first time in a middle-aged person with a positive serologic reaction for syphilis; or 3, a diffusely dilated aorta without aortic regurgitation or hypertension, past or present.

Maynard<sup>124</sup> discusses the clinical and the roentgen aspects of the diagnosis of uncomplicated aortitis, deriving six diagnostic criteria: 1. The patient must be 40 years of age or younger. 2. He must have had syphilis beyond reasonable doubt. 3. There must be roentgen or fluoroscopic evidence of a dilated aorta. 5. There may be a hollow accentuated aortic second sound. 6. There may be a systolic murmur at the aortic area. Widened retromanubrial dullness, precordial "aortalgia" and a history of cardiac embarrassment are all discounted as of little value in early diagnosis.

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124. Maynard, E. P., Jr.: The Present Status of the Diagnosis of Uncomplicated Syphilitic Aortitis, *Bull. New York Acad. Med.* **18**:383 (June) 1942.

*Syphilitic Aortic Regurgitation.*—McDermott, Tompsett and Webster<sup>125</sup> call attention to the fact that the average picture of aortic insufficiency described in standard textbooks is one of rapid development of symptoms and signs of cardiac insufficiency in a patient in the forties or the fifties. It is usually agreed that survival from this age on is usually a matter of only one or two years. In contrast to this generally accepted view, the authors point out that Grant, when studying 1,000 patients with cardiac disease ten years after the original examination, showed that the ten year mortality associated with syphilis of the aortic valve is only 64 per cent, actually less than the mortality rate over the same period in patients with mitral stenosis with auricular fibrillation (68 per cent).

The discrepancy between the longevity in Grant's series and that in the reports from many of the better syphilis clinics of the country can be explained on the basis of the patients examined. Grant's patients were all white, ambulatory and military pensioners, whereas the reports from various syphilis clinics were based on patients with aortic insufficiency, who usually reported to these clinics because of cardiac symptoms.

The authors report on the study of 2,718 syphilitic patients who were examined during the four and a half year period from October 1936 to April 1941. They summarize their results as follows:

1. In a 4½-year period in the syphilis division of the medical clinics of the New York Hospital, the incidence of syphilitic aortic insufficiency without aneurysm was 3.4% (91 of 2718).

2. One-half of these patients (49.5%) with aortic regurgitation denied any symptoms of cardiac insufficiency at the time of diagnosis.

3. Only 31 (34%) of the 91 patients sought medical care because of symptoms referable to the heart, 53 (58%) sought care for non-cardiac complaints, and 7 (8%) were brought under medical care by the routine serologic testing of supposedly well people.

4. Of 28 of these asymptomatic patients followed for more than 2 years, 2 have died of heart disease and only 2 have developed symptoms.

5. Circulatory studies (vital capacity, venous pressure, circulation time and roentgenoscopy) of 47 of these patients showed a close correlation with the clinical impression of their cardiac status.

6. The aortic width, as judged from Roentgen ray and fluoroscopy, was normal in 37 of 87 (43%) of these patients with aortic insufficiency.

7. In only 3 patients (2.2%) of a total of 135 with syphilitic aortic insufficiency was the blood Wassermann reaction negative in the absence of a history of previous antisyphilitic treatment.

The authors therefore suggest that syphilitic aortic insufficiency is frequently present in clinically recognizable form for long periods before

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125. McDermott, W.; Tompsett, R. R., and Webster, B.: Syphilitic Aortic Insufficiency: The Asymptomatic Phase, *Am. J. M. Sc.* **203**:202 (Feb.) 1942.



the development of symptoms and that the prognosis as to average duration of life is better than is usually believed.

According to Sprague,<sup>126</sup> the absence of left axis deviation in the electrocardiograms of patients with syphilitic aortitis suggests a complication beyond simple aortic regurgitation. Conditions resulting in acute or chronic strain on the left ventricle or conditions resulting in an additional strain on the right ventricle are largely responsible for a normal electric axis or right axis deviation. In patients with bundle branch block considerable coronary obstruction may be present. Sprague believes the electric axis of the electrocardiogram to be of more use than the ST and the T segment in indicating complications of syphilitic aortitis. The results of his study emphasize again that the extent of the disease process and the presence of complications are of more importance than the etiologic factor alone in the production of alterations in the electrocardiogram.

*Flint's Murmur.*—An explanation of the mechanism of Flint's murmur acceptable to many clinicians is that blood regurgitating through a damaged aortic valve strikes against the anterior mitral curtain and pushes it laterally into the auriculoventricular blood stream. As a result, a functional obstruction is created at the mitral valve. The anterior mitral leaflet, displaced from its usual position in diastole, now hangs suspended between two down flowing streams of blood and is impinged on by both; therefore, vibrations are set up which cause the rumbling presystolic apical murmur of aortic regurgitation. Since only a small number of patients with aortic regurgitation have a Flint murmur, it is probable that some anatomic or physiologic difference occurs in those who do have such a murmur.

A lesion involving the posterior aortic leaflet has generally been thought to be responsible for Flint's murmur. This assumption was based on experimental aortic regurgitation produced in dogs by operative perforation and laceration of the posterior aortic leaflet. After this operation, 36 per cent of the dogs had a diastolic apical murmur and a diastolic apical thrill.

Gouley<sup>127</sup> describes the pathologic changes noted in the aortic and the mitral valve in 10 cases of aortic insufficiency with an associated Flint murmur. In the majority of cases the patients had cardiovascular syphilis. Five cases are discussed in detail. In all cases the right aortic leaflet presented a concave cup-shaped deformity of its inner portion; this inner portion sagged, and the free margin pouched or

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126. Sprague, H. B.: Syphilitic Aortitis with Aortic Regurgitation: An Electrocardiographic and Autopsy Survey at the Massachusetts General Hospital, J. Mt. Sinai Hosp. 8:1034 (Jan.-Feb.) 1942.

127. Gouley, B. A.: Aortic Valvular Lesion Associated with Austin Flint Murmur, Am. Heart J. 22:208 (Aug.) 1941.

drooped outward into the ventricular lumen. The other leaflets were either normal or only slightly involved. Also noted was the thickening of the anterior mitral curtain on its ventricular aspect. In some cases the lower half of the curtain, including the site of attachment of the chordae tendineae, showed an almost uniform increase in thickness and opacity. Usually, this was notable at the inner and the lower portion of the curtain. Endocardial sclerosis also involved the mural endocardium of the adjacent ventricular septum.

*Infarction in Syphilitic Heart Disease.*—In Garvin's<sup>128</sup> study of the incidence of embolic manifestations in various forms of heart disease, 25 of 67 patients with syphilitic heart disease were found on postmortem examination to have infarcts in various organs, an incidence of 37.3 per cent. Infarcts were most frequently noted in the lungs and the brain.

*Syphilitic Myocarditis.*—In a comprehensive review of the general subject of myocarditis Saphir<sup>129</sup> has discussed the pertinent literature and his own extensive experience with the controversial subject of syphilitic involvement of the myocardium. In his opinion the crux of the question lies in the unequivocal demonstration of *S. pallida*, for he does not feel that it is justifiable to attribute a specific cause to non-specific histologic lesions, such as those often noted in the myocardium. He concludes that diffuse syphilitic inflammation with the presence of spirochetes in acquired syphilis is extremely rare, if it occurs at all, and suggests the need for more thorough histopathologic studies with confirmation by animal inoculations.

*Aortic Aneurysm as a Cause of Obstruction of the Venous Circulation of the Mediastinum.*—Aortic aneurysm is mentioned by Hinshaw and Rutledge<sup>130</sup> as among the lesions in the superior mediastinum which interfere with venous circulation. In 2 of the 22 cases observed by them obstruction was due to this cause.

*Rupture of Aortic Aneurysm into the Pulmonary Artery.*—Current textbooks on medicine, physical diagnosis and cardiology contain few accurate data on the clinical course and the physical phenomena of a fistulous opening between an aortic aneurysm and the pulmonary artery. According to Porter,<sup>131</sup> this syndrome was nearly perfectly described

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128. Garvin, C. F.: Infarction in Heart Disease, *Am. J. M. Sc.* **203**:473 (April) 1942.

129. Saphir, O.: Myocarditis: A General Review, with an Analysis of Two Hundred and Forty Cases, *Arch. Path.* **33**:88 (Jan.) 1942.

130. Hinshaw, H. C., and Rutledge, D. I.: Lesions in the Superior Mediastinum Which Interfere with Venous Circulation, *J. Lab. & Clin. Med.* **27**:908 (April) 1942.

131. Porter, W. B.: The Syndrome of Rupture of an Aortic Aneurysm into the Pulmonary Artery, *Tr. A. Am. Physicians* **56**:201, 1941.

by Hope in 1833. In the present paper 3 cases of such a condition are reported in detail. The criteria for the syndrome are summarized as follows:

Continuous and severe breathlessness.

The physical phenomena of pulmonary stasis are slight in proportion to the intensity of the dyspnea.

Preponderance of right heart failure, which develops immediately after the onset of the acute respiratory distress.

Cyanosis is not a significant phenomenon.

A purring systolic and diastolic thrill over the base of the heart [most intense during the systolic phase]. . . .

A long, harsh, continuous murmur with the point of maximum intensity at the third inter[costal] space 1 to 3 cm. to the left of the sternal margin. The systolic phase of the murmur is peculiarly harsh and long, while the diastolic phase is short in duration and transmitted downward for only a few centimeters along the left sternal margin. The murmur is best heard with the patient in a sitting posture and leaning slightly forward.

Absence of an Austin Flint . . . murmur.

The peripheral arterial phenomena of free aortic insufficiency.

Physical and roentgenographic evidence of aneurysm of the ascending aorta.

Cardiac enlargement, but not classically aortic in type.

The electrical axis of the electrocardiogram may progress to a right axis deviation.

The stethogram shows a murmur similar in its essential details to that of a patent ductus arteriosus.

White, Chamberlain and Kelson<sup>132</sup> have also discussed the syndrome of rupture of an aneurysm of the aorta into the pulmonary artery. In 6 of the 13 cases reported in the literature in the last twenty-five years the patients were Negroes; in only 5 did the patients live more than two months after the onset of symptoms. The case observed by the authors was unusual in that the patient survived twenty-one months. The clinical diagnosis was apparent from the combination of the development of a continuous murmur in the area of the pulmonary valve, the bulging pulmonary artery visible on roentgen examination and the rapid appearance of congestive heart failure, without early fatality, in a Negro with known syphilitic aortitis.

#### SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

*Management of Neurosyphilis.*—Dattner and Thomas<sup>133</sup> outline the management of patients with syphilis of the central nervous system. In their experience the type of involvement of the central nervous system is less important than the activity of the neurosyphilitic process.

132. White, P. D.; Chamberlain, F. L., and Kelson, S. R.: Rupture of Aorta into Pulmonary Artery with Long Survival, *Ann. Int. Med.* **15**:589 (Sept.) 1941.

133. Dattner, B., and Thomas, E. W.: The Management of Neurosyphilis. *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:21 (Jan.) 1942.

In determining activity the appearance of new clinical manifestations and the results of examination of the spinal fluid, especially increases in cells and in proteins, are considered reliable guides. The authors recommend the institution of fever treatment as soon as possible after the diagnosis is made in every case in which examination of the spinal fluid indicates an active neurosyphilitic process and discuss the relative merits of inoculation of malaria parasites, intravenous administration of typhoid vaccine and production of fever by physical means. Chemotherapy following the fever treatment is advised, and the authors report the relative safety of giving ten daily injections of 0.06 Gm. of mapharsen immediately after the last episode of malarial fever. They decry unnecessary prolongation of chemotherapy following fever and recommend examinations of the spinal fluid for evidence of activity of the neurosyphilitic process at intervals of six months.

*Syphilitic Trigeminal Neuritis.*—Strauss<sup>134</sup> describes 4 cases in which exquisite tenderness of the masseter and the temporal muscles was encountered in patients with syphilitic trigeminal neuritis. The muscle tenderness and other signs of involvement of the fifth nerve disappeared with antisyphilitic therapy. The presence of such muscle tenderness with trigeminal neuritis should suggest syphilis as the etiologic factor.

*Syphilis of the Spinal Cord.*—King<sup>135</sup> has discussed in detail seven lesions of the spinal cord due to syphilis (vascular occlusion, meningo-myelitis, Erb's spastic paraplegia, progressive muscular atrophy, gumma, hypertrophic cervical pachymeningitis and tabes dorsalis) and one due to arsenotherapy (hemorrhagic myelitis). He concludes:

The following clinical syndromes are due to syphilitic involvement of the cord:

1. Large vascular accidents involving the spinal arteries are an unusual condition. The best known example is thrombosis of the anterior spinal artery. The signs are a segmental loss of pain, temperature and other manifestations of injury to the anterior horn cells, with varying amounts of damage to the ascending spinothalamic and descending pyramidal tracts. The acute paraplegias of syphilis are also due to vascular occlusions, and they may be followed by a partial return of function. This is an early manifestation of spinal cord syphilis. Any portion of the cord may be involved, without predominance at any point.

2. A diffuse meningomyelitis, often associated with small vascular occlusions, is also seen early in the disease. This form is a more common variety. Pain, due to root irritation, is a frequent feature. The upper thoracic cord is most often affected, and girdle pains are characteristic. The process often subsides spontaneously, and even more rapidly with treatment. Residua are usually few.

3. Erb's spastic paraplegia is a late form of syphilitic myelitis. The pyramidal tracts are most severely damaged, with only mild injury to other parts of the cord.

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134. Strauss, I.: Masseter and Temporal Muscle Tenderness in Syphilitic Trigeminal Neuritis, J. Mt. Sinai Hosp. 8:1060 (Jan.-Feb.) 1942.

135. King, A. B.: Syphilis of the Spinal Cord, Am. J. Syph., Gonorr. & Ven. Dis. 26:336 (May) 1942.

Besides the spastic paraplegia, there are frequently bladder disturbances. The syndrome is very slow in development and the middle thoracic cord alone is involved. Treatment is generally unsatisfactory.

4. Progressive muscular atrophy is also a late complication. Here the anterior horn cells are the principal site of injury. The lower cervical cord is the most frequent location for the variety of spinal cord syphilis. Muscular atrophy and fasciculations are the usual clinical findings. Amyotrophic lateral sclerosis is a closely associated condition in which there is injury to the pyramidal tracts as well as to the anterior horn cells. There is a continual gradation between the two syndromes. Therapy is effective in halting the process.

5. Gummas may occur after the first year of infection. The signs are those of cord neoplasm. Any portion of the cord or cauda equina may be the site of the granuloma. The results of therapy are usually good. However, there is one special form of massive, chronic gummatous process which is limited to the cervical region, known as hypertrophic cervical pachymeningitis. Symptoms and signs may be those of a mass, but they may simulate those of syringomyelia or amyotrophic lateral sclerosis. It is very resistant to treatment.

6. Tabes dorsalis is a process in which the sensory roots alone are damaged, resulting in ataxia, loss of reflexes, bladder disturbances, characteristic gait, and various forms of pain. It is usually a late complication of syphilis. One or several cranial nerves may be injured concurrently. While the site of the lesion is clear, its mode of production is not. It is not usual to find the blood and spinal fluid serologic tests for syphilis negative. The sacral portion of the cord is most frequently involved, with a slow, steady upward spread. Treatment may halt the process, and at times give relief from pain.

7. Hemorrhagic myelitis is included because it may be a complication of arsphenamine therapy, which is used extensively in the treatment of syphilis. Arsenic alone is probably responsible for the damage to the cord. The lesion is essentially capillary damage produced by arsenical drugs which result in minute hemorrhages in the substance of the cord. Usually the patients sustain a complete transverse myelitis. This complication of therapy is rare, and it frequently occurs after the second dose of arsphenamine. The thoracic cord is most often affected. Recovery is variable and rarely complete. Therapy is ineffectual.

*Encephalographic Studies.*—Electroencephalography has as yet not advanced beyond the descriptive stage. The ultimate goal of investigators in this field is to correlate electroencephalographic patterns with neurophysiologic processes. Only if such studies are made on lesions of the central nervous system of known types and locations will there be definite progress in this field. For this reason, Finley, Rose and Solomon<sup>136</sup> report encephalographic studies on patients with syphilis of the central nervous system.

The results of the study can best be described by quoting the authors' summary and conclusions.

1. Electroencephalographic records were obtained from 175 patients with neurosyphilis, in 124 of whom the condition was diagnosed as dementia paralytica, in 20 as tabes dorsalis, in 11 as juvenile dementia paralytica, in 8 as optic nerve atrophy

136. Finley, K. H.; Rose, A. S., and Solomon, H. C.: Electroencephalographic Studies on Neurosyphilis, *Arch. Neurol. & Psychiat.* 47:718 (May) 1942.

and in 12 as meningovascular neurosyphilis. These tracings are compared with the records from 215 normal controls.

2. Normal electroencephalographic tracings were found for 19 per cent of the patients (treated and untreated) and for 70 per cent of the controls. Borderline records were found for 28 per cent of the patients and for 23 per cent of the controls. Abnormal records were found for 53 per cent of the patients and for 7 per cent of the controls.

3. Abnormal electroencephalographic tracings were as common among patients with pure tabes and those with optic nerve atrophy as among patients with dementia paralytica.

4. The records of 73 untreated patients with dementia paralytica showed a higher percentage of borderline and abnormal patterns than the records of 63 patients who had received treatment for nine months or more.

5. No characteristic electroencephalographic pattern was found to be associated with neurosyphilis or with any type of neurosyphilis. The electroencephalogram has therefore no significant diagnostic value.

6. The 73 untreated patients with dementia paralytica presented a degree of abnormality in the electroencephalogram which corresponded roughly with the clinical severity of the disease.

7. Follow-up electroencephalographic records on many of the patients undergoing treatment with clinical improvement are presented. In most instances there was concurrent improvement in the electroencephalographic tracings.

8. Electroencephalograms with abnormally slow, high voltage cycles were more likely to be found among patients with dementia paralytica who showed confusion, disorientation and profound memory loss, while rapid cycles were more common among those with euphoria or other mood disturbances and paranoid ideas without the aforementioned signs. Slow cycles indicated more serious cerebral dysfunction than did rapid cycles.

9. The majority of abnormal patterns associated with all types of neurosyphilis were similar from homologous areas of the two hemispheres. This observation, together with the fact that abnormal records were as frequent in cases of pure tabes and optic nerve atrophy, suggests that lesions in or near the upper portion of the midbrain and the diencephalon may have more to do with the abnormal cortical electrical potentials than the cortical lesions.

*Malaria Inoculata in Therapy of Neurosyphilis.*—Since 1925 1,026 patients have been treated with inoculation malaria at the University of Michigan Hospital, with 29 deaths occurring either during paroxysms or immediately following their termination, a mortality rate of 2.8 per cent. Wile and Mundt<sup>137</sup> have studied the cause of death in this group of patients.

Of the 29 deaths, peripheral circulatory collapse accounted for 12 (41 per cent); pneumonia, 5 (17 per cent); hyperpyrexia, 5 (17 per cent), and suicide, 2 (7 per cent), while there was 1 (3 per cent) death each from erysipelas, cerebral thrombosis, bleeding duodenal ulcer, ruptured spleen and respiratory failure with convulsions. Thirty-

137. Wile, U. J., and Mundt, L. K.: An Analysis of Deaths Following Therapeutic Malaria, *Am. J. Syph., Gonorr. & Ven. Dis.* 26:181 (March) 1942.

five per cent of the patients had dementia paralytica, while these patients accounted for 66 per cent of the deaths. From this the authors conclude that the risk associated with dementia paralytica is apparently greater than that associated with other types of syphilis of the central nervous system.

On the basis of their analysis the same authors<sup>138</sup> have outlined the proper management of patients inoculated with therapeutic malaria in order to avoid fatal complications, discussing briefly the various contraindications, precautions and complications, together with the management of serious complications.

*Chemotherapy of Malaria.*—New chemotherapeutic agents for the treatment of malaria continue to appear. Two new remedies have been tested by Coggeshall, Maier and Best.<sup>139</sup> They state:

Seventeen patients acutely ill with vivax and falciparum malaria were treated with sodium p,p'-diaminodiphenylsulfone N,N'-didextrose sulfonate (promin). The results revealed a definite effect on naturally acquired human malaria infections. The vivax infections were more resistant to therapy than the falciparum. The infections in the native Negro residents were more responsive to the drug than the same infections in the relatively nonimmune white patients.

Thirteen patients with vivax, falciparum and quartan malaria were treated with 2-sulfanilamido pyrimidine (sulfadiazine). There was a demonstrable effect in 10 cases but none in 3. Although the effect of this drug was definite, it appeared to be less active than promin when given under the conditions described.

From the observations cited, it seems apparent that there is ample evidence to show that these new types of compounds, unrelated to quinine or atabrine, possess considerable activity against experimental and human malaria and, with related compounds, justify further study.

It should be emphasized that at present there are no reasons for giving the drugs in preference to quinine or atabrine for the treatment of malaria, and they should be regarded only as important substitutes.

*Artificial Fever Therapy of Neurosyphilis.*—Lopez<sup>140</sup> reports the treatment of 5 patients with dementia paralytica with fever induced by inoculation with the spirochete of Mexican relapsing fever and claims improvement in the mental symptoms occurred in all patients so treated.

Nielson, Marx and Dickel<sup>141</sup> have treated 5 patients suffering from juvenile neurosyphilis with artificial fever therapy and subsequent

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138. Wile, U. J., and Mundt, L. K.: Avoidance of Fatal Complications in Therapeutic Malaria, *Arch. Dermat. & Syph.* **44**:1078 (Dec.) 1941.

139. Coggeshall, L. T.; Maier, J., and Best, C. A.: The Effectiveness of Two New Types of Chemotherapeutic Agents in Malaria: Sodium P,P'-Diaminodiphenylsulfone N,N'-Didextrosesulfonate (Promin) and 2-Sulfanilamido Pyrimidine (Sulfadiazine), *J. A. M. A.* **117**:1077 (Sept. 27) 1941.

140. Lopez, S.: Infeccion experimental de spirochaeta turicatae de México, en enfermos de parálisis general, *Rev. d. Inst. de salub. y enferm. trop.* **3**:41, (March) 1942.

141. Nielson, J. C.; Marx, J. R., and Dickel, H. A.: Artificial Fever Therapy in Juvenile Neurosyphilis, *Arch. Dermat. & Syph.* **45**:688 (April) 1942.

chemotherapy. One patient died during treatment, but the rest showed physical and mental improvement during an observation period of one to three and a half years. The authors believe the results from the use of artificial fever therapy in the treatment of juvenile neurosyphilis compare favorably with those obtained by other investigators with malaria therapy.

An improved method of obtaining sustained controlled hyperpyrexia with triple typhoid vaccine is reported by Solomon and Somkin.<sup>142</sup> Although their paper describes a method of fever therapy used in 14 cases of subacute bacterial endocarditis, the method is applicable to the treatment of syphilis of the central nervous system. By giving triple typhoid vaccine slowly by the intravenous drip method, it was possible more or less to hold the temperature at any desired level for as long a time as was thought necessary.

The method as described by the authors is as follows:

The patient can be treated in his hospital bed; he must be well covered to minimize heat loss. . . . Triple typhoid vaccine in amounts equal to that ordinarily used in the first of a series of typhoid shock therapy injections is added to 1,000 cc. of sterilized normal saline. This is thoroughly mixed and added to the sterilized infusion flask which usually has a capacity of 300 cc. This flask is agitated from time to time to insure an even suspension of organisms. The site of preference for insertion of the needle is a forearm vein. . . . The infusion is started at the slowest rate of flow possible (20 to 25 drops per minute). The chill usually occurs within 35 to 45 minutes, and can be suppressed to a considerable extent by injecting into the infusing tubing at the onset of the symptoms, morphine sulfate (.015 Gm.) and calcium gluconate or chloride (1 Gm.). If, as occasionally happens, there is no sign of a chill in 45 minutes, the infusion rate may be doubled. From this point on the temperature may be sustained at the effective level of about 104° F. for as long as 6 to 10 hours without further chills. The maximum temperature elevation usually occurs within 1½ hours after the chill. Rectal temperatures every 10 to 15 minutes are quite important at that time. The infusing rate should not be increased by more than 2 times until the temperature has reached a constant level or has begun to fall. At that time the rate of flow may again be doubled or more feasibly an infusing solution with a greater number of killed organisms may be substituted. As a general rule, the longer the temperature has been elevated the greater the number of organisms or drops per minute required to maintain the temperature at 104° F. . . .

Elevations or depressions in the temperature can be obtained within 10 to 25 minutes by increasing or decreasing the rate of flow. Excessive rises are controlled by sponging, exposing the limbs or antipyretics. Once the infusion is discontinued, the temperature drops rapidly. Replenishing solutions should usually contain twice the number of organisms as the initial solution. Morphine sulfate (.015 Gm.) is given intravenously every 3 to 4 hours for restlessness. In carrying out a series of treatments every day or every other day, the number of organisms used is

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142. Solomon, H. A., and Somkin, E.: An Improved Method of Obtaining Sustained Controlled Hyperpyrexia with Triple Typhoid Vaccine, *Am. J. M. Sc.* 203:736 (May) 1942.



determined in a manner similar to that of the single injection technique, namely, .02 or .03 cc. of triple typhoid vaccine for the first, .1, .2, .4 cc. and so on for the succeeding ones.

It is wise to start with a very small number of organisms for the first treatment as there is often a prolonged febrile response and a secondary rise lasting 1 to 2 days. For this reason, we are inclined to feel that since the first injection with its variable response is so often apt to give but a poor temperature elevation, it is simpler to administer only 1 injection of triple typhoid vaccine for the first session. The temperature elevation should be allowed to subside before starting the next treatment. The infusion should not be continued for longer than 6 hours until the febrile responses are properly gauged. . . .

*Combined Fever Therapy and Chemotherapy.*—An extensive critical review of the treatment of syphilis with artificial fever combined with chemotherapeutic agents has appeared as a supplement to *Venereal Disease Information*. The results of the ten years' experience of the authors, Simpson, Kendell and Rose,<sup>143</sup> with the method, together with information included in reports to them by other investigators with experience in the field, is summarized as follows:

1. After a decade of rich and constantly enlarging experience with physically induced artificial-fever therapy, the successful results achieved by many workers in many lands are sufficiently comparable to justify the categorical statement that artificial-fever therapy is at least as effective as malarial therapy in the management of symptomatic or asymptomatic neurosyphilis. In the hands of many reliable investigators artificial-fever therapy has yielded significantly superior results. Patients who have not responded well to malarial therapy have been benefited by subsequent artificial-fever therapy.

2. There is unmistakable evidence that the extent of clinical improvement in neurosyphilitic patients is related directly to the height and the duration of fever. . . . There is no longer any valid reason to assume that the malarial plasmodium exerts any specific effect upon *Spirochaeta pallida*.

3. Several investigators who have had long experience with malarial therapy and with artificial-fever therapy have abandoned malarial therapy in favor of artificial-fever therapy. This decision was determined largely by the observations that (a) patients tolerate artificial-fever therapy more readily, (b) a high proportion of neurosyphilitic patients can be treated with artificial fever on an ambulatory basis without interruption of gainful employment, and (c) treatment complications are minimized with artificial-fever therapy.

4. Since continuous hospitalization is not a requirement for treatment with artificial fever of most neurosyphilitic patients, the cost of the treatment is not necessarily greater than with malarial therapy. If the patient remains at his regular employment during the course of artificial-fever therapy, the cost is usually much less.

5. The employment of auxiliary chemotherapy in conjunction with any type of fever therapy is an essential requirement. There is evidence that the concurrent

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143. Simpson, W. M.; Kendell, H. W., and Rose, D. L.: The Treatment of Syphilis with Artificial Fever Combined with Chemotherapy: Results of Ten Years Experience, *Ven. Dis. Inform.*, 1942, supp. 16.

use of chemotherapy with artificial-fever therapy increases the therapeutic effectiveness of both agencies.

6. The hazards inherent in the various physical modalities used for the production of artificial fever during the first few years of the undertaking have been largely eliminated. . . .

7. Developments of the past few years have demonstrated that equally favorable clinical and serologic results may be obtained with fewer total hours of artificial-fever therapy, applied in shorter individual sessions at more frequent intervals. This practice permits the treatment of more patients at less cost.

8. The excellent results following the use of combined fever-chemotherapy in cases of asymptomatic neurosyphilis indicate that the patient's best interests are served by the prompt administration of this form of treatment.

9. The exudative forms of ocular syphilis, in contrast to the degenerative lesions, usually respond promptly and favorably to combined artificial fever-chemotherapy. Procrastination should be avoided in administering fever therapy in cases of exudative ocular syphilis in which chemotherapy is ineffective. There is reason to believe that primary optic atrophy may sometimes be improved or arrested by fever-chemotherapy.

10. The addition of artificial-fever therapy to the program of chemotherapy will produce serologic reversal in the majority of patients with resistant seropositive latent syphilis.

11. The general recognition of the inadequacies of present-day chemotherapeutic programs in the management of early syphilis has led to investigations of the possible usefulness of artificial-fever therapy combined with chemotherapy in such cases. There is a growing body of evidence which indicates that artificial fever intensifies and fortifies the effectiveness of antisyphilitic chemical compounds. It seems possible that the time, effort, and expense required for the eradication of early syphilis may be lessened as the result of future researches in this direction. At the present time such methods of treatment should be considered strictly experimental. The results achieved thus far, however, should stimulate other investigators to engage in long-term, controlled experiments with a view to the introduction of more rapid, more certain, less dangerous, and less costly methods of treatment.

12. In the hands of skilled and devoted workers, artificial-fever therapy provides the venereologist with a potent therapeutic weapon.

*Metrazol Shock Therapy of Psychoses Associated with Dementia Paralytica.*—It is a not uncommon clinical experience in the treatment of patients with dementia paralytica that despite improvement in the abnormal condition of the spinal fluid a patient may remain psychotic. Attempting to benefit this group of patients, Kenyon, Lôzoff and Rapaport<sup>144</sup> have treated 16 psychotic patients with metrazol. Twelve of these patients had previously received fever therapy; 4 had not had such treatment. After convulsions induced by metrazol, 2 of the fever-treated patients were improved sufficiently to be paroled, 5 others were improved somewhat and the remaining 5 did not receive any

144. Kenyon, V. B.; Lozoff, M., and Rapaport, D.: Metrazol Convulsions in the Treatment of the Psychosis of Dementia Paralytica, Arch. Neurol. & Psychiat. 46:884 (Nov.) 1941.

benefit. No particular danger was noted in inducing metrazol convulsions in patients with dementia paralytica, and their reactions simulated those of patients with functional psychoses. The authors feel that metrazol shock therapy is warranted in those instances of dementia paralytica in which the psychosis does not respond to the usual treatment, including hyperpyrexia.

*Vitamin Therapy of Tabes Dorsalis.*—It is now generally accepted that all patients with tabes dorsalis have syphilitic involvement of the central nervous system, but there is some doubt as to whether all the signs and symptoms of the tabetic patient are due entirely to syphilis. Several recorded experiments in animals suggest that certain dietary constituents are required for maintaining normal myelination.

Stone<sup>145</sup> has treated 18 patients with advanced tabes dorsalis with the vitamin B complex, vitamin B<sub>1</sub> and vitamin E for periods ranging from three months to two years. Seventeen of the 18 patients received intraspinal injections of thiamine hydrochloride in doses ranging from 10 to 50 mg., with one to six treatments per patient. All of them also received vitamin B complex and wheat germ oil orally. Definite improvement is recorded in gait, muscle strength and tone, coordination, function of the bladder, reduction of frequency of gastric crises and lightning pains. Neither severe reaction nor death resulted from the treatment. Intraspinal administration of thiamine hydrochloride and oral administration of vitamin E and the vitamin B complex may be used concurrently with fever therapy or arsenotherapy. Stone believes that the therapeutic results of fever are enhanced and that tolerance to arsenic and heavy metals is increased thereby.

*Degeneration of the Spinal Cord Produced Experimentally by Dietary Means.*—Mitchell<sup>146</sup> was able experimentally to produce ataxia and demyelination of the posterior roots in young pigs fed a synthetic diet which supplied normal growth requirements. These changes could not be related to any vitamin deficiency, and the author suggests that the abnormalities of the posterior column were due to a lack of some essential inorganic microconstituent of the diet, possibly copper, rather than to a want of any known vitamin.

Sullivan and his co-workers<sup>147</sup> have produced experimentally a generalized pruritic exfoliative dermatitis in young rats fed a ration

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145. Stone, S.: Vitamin B and E Therapy in Tabes Dorsalis, *J. Nerv. & Ment. Dis.* **95**:156 (Feb.) 1942.

146. Mitchell, D.: Spinal Cord Degeneration Produced by Dietary Means: Demyelination of Posterior Roots in Young Pigs Fed Synthetic Diet Which Supplied Normal Growth and Appeared to Be Biologically Complete, *Brain* **64**: 165 (Sept.) 1941.

147. Sullivan, M.; Kolb, L., and Nicholls, J.: Nutritional Dermatoses in the Rat: VII. Notes on the Posture, Gait and Hypertonicity Resulting from a Diet Containing Unheated, Dried Egg White as the Source of Protein, *Bull. Johns Hopkins Hosp.* **70**:177 (Feb.) 1942.

containing uncooked egg white. At the height of the dermatitis abnormal posture, abnormal gait and hypertonicity were usually observed. After several days of treatment with biotin concentrates or foodstuffs containing biotin (vitamin H concentrate) the last-mentioned signs were rapidly alleviated.

*Neurogenic Bladder.*—Emmett and Beare<sup>148</sup> briefly discuss the theoretic considerations of disturbances of the bladder associated with tabes dorsalis and point out that it is only necessary to read the scanty literature on vesical disturbances in this disease to realize that the subject is still one of the mysteries of medicine. This study is based on the case records of 977 patients with a condition given the diagnosis of tabes dorsalis at the Mayo Clinic during the seven year period 1934 to 1940, inclusive. Seventy-nine per cent of this group were males, and 21 per cent females. The majority of patients, 670 (69 per cent), were in the age groups from 40 to 59 years. Of the entire group of 977 patients, 419 (42.8 per cent) complained of symptoms referable to the urinary bladder.

These symptoms complained of by the 419 patients (74 females, 345 males) are listed; the most commonly observed were incontinence, hesitancy, poor stream, nocturia, terminal dribbling, frequent desire to void and inability to tell when the bladder was full. Aside from incontinence and inability to tell when the bladder was full, the symptoms in the males were those commonly associated with obstruction of the vesical neck. Many of the patients in the series did not have residual urine measured, but in general, residual urine was more common in the males than in the females. Of the 196 male patients who were catheterized, only 77 had more than 150 cc. of residual urine. Only 150 male patients complained of incontinence; since only 77 of these were found to have more than 150 cc. of residual urine, certainly not more than 50 per cent of incontinence was due to the overflow type.

The authors then discuss various types of incontinence and point out that in persons with continuous leakage there is frequently retention of more than 150 cc. of urine, and therefore incontinence in these patients probably is of the so-called overflow type.

Only 129 of the 419 patients were subjected to cystoscopic examination. The size of the trabeculae in the bladders of these patients varied greatly. The old dictum that there are fine trabeculae in a neurogenic bladder and coarse trabeculae in a bladder obstructed at the vesical neck may be seriously questioned. Of the 111 male patients subjected to cystoscopic examination, 61 (55 per cent) had definite obstruction

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148. Emmett, J. L., and Beare, J. B.: Bladder Difficulties of Tabetic Patients, with Special Reference to Treatment by Transurethral Resection, J. A. M. A. **117**:1930 (Dec. 6) 1941.

of the vesical neck. This was due in 49 instances to lobar hypertrophy; in 10 to median bars, contractures of the vesical neck or carcinoma, and in 2 to various combinations of the conditions in the two preceding groups. The incidence of relaxation of the vesical neck in the incontinent group was somewhat higher.

Of the 345 male patients who had vesical symptoms, 35 were subjected to transurethral prostatic resection. In some cases the urinary retention resulted from a simple obstruction of the vesical neck and *tabes dorsalis* was purely coincidental. In the majority, however, it was difficult to decide whether vesical dysfunction was the result of primary neurogenic atony, obstruction of the vesical neck with secondary atony or a combination of the two.

The results of transurethral resection were gratifying. Residual urine was eliminated in almost all cases. Of the 13 patients in this group who suffered from incontinence prior to operation, 11 were completely relieved of this condition and 2 were considerably helped. Incontinence was never produced by the operation itself. The authors believe that there is no more danger of incontinence following transurethral resection in patients with *tabes dorsalis* than in patients with other conditions. In the group subjected to surgical procedures were 19 patients in whom it was felt that part if not all of the vesical dysfunction was due to *tabes*. However, 15 of these patients obtained excellent results, and the condition in 4 was definitely improved. The authors say:

As far as the subject of incontinence is concerned, it seems to us that this condition in cases of *tabes dorsalis* is chiefly of two general types, (1) overflow from a distended bladder and (2) intermittent involuntary urination or the occasional loss of a small amount of urine before micturition takes place. This urine is lost apparently because there is so much sensory loss that the patient is not aware the micturition is about to begin. . . .

We have no clinical data that would tend to confirm the theory that increased tone of the external urethral sphincter of tabetic patients may contribute to the urinary retention and difficult micturition. All of the data obtained from this study point to the fact that fibrosis or contracture of the internal (vesical) sphincter or obstruction in this situation produced by the enlargement of the prostate gland is more likely to be responsible. If any obstruction is present, transurethral resection of the vesical neck will yield brilliant results in many cases. As far as we are aware, any local treatment of the external urethral sphincter has been of no benefit in any of these cases. Any tabetic patient who has difficulty in voiding, incontinence (especially of the overflow variety), residual urine and some demonstrable obstruction of the vesical neck has an excellent chance of relief of symptoms by complete transurethral resection. . . .

Nesbit and Gordon<sup>149</sup> believe that in the autonomous neurogenic bladder the detrusor muscles become hypertonic and that the circularly

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149. Nesbit, R. M., and Gordon, W. G.: Surgical Treatment of Autonomous Neurogenic Bladder, *J. A. M. A.* **117**:1935 (Dec. 6) 1941.

arranged fibers at the neck of the bladder described as the internal sphincter share in the hypertonicity of these muscles. In their opinion this hypertonic internal sphincter acts as a definite obstruction, analogous to contracture of the vesical neck. As a result of this condition urine cannot escape from the bladder until the intravesical pressure exceeds the obstruction at the outlet. The authors believe that since nothing can be done about restoring the destroyed innervation of the neurogenic bladder, surgical treatment should be aimed at removing the obstructive factor. They summarize as follows:

The autonomous neurogenic bladder results from destructive lesions of the conus terminalis and cauda equina. Since the internal sphincter shares in the hypertonicity of the bladder, it acts as an outlet obstruction. As with any outlet obstruction, bladder decompensation and damage to the upper urinary tract will ultimately result if the condition persists for a sufficiently long time.

Modern treatment of the autonomous neurogenic bladder attempts to relieve the outlet obstruction. Presacral neurectomy has not proved satisfactory in our experience. Transurethral sphincterotomy yields more gratifying results, particularly if undertaken before the bladder has decompensated.

*Surgical Treatment of Optic Chiasm Arachnoiditis.*—Schaub,<sup>150</sup> discussing the surgical treatment of optic chiasm arachnoiditis due to syphilis, states that in the past two years he has encountered 10 cases in which the diagnosis of this condition was verified at operation. In all cases the decline of visual acuity and visual fields, together with ophthalmoscopic signs of atrophy, were rapidly progressive, and in 9 of the 10 cases the process was arrested by operation. Schaub believes that no patient with failing vision due to syphilitic atrophy of the optic nerve should be permitted to go blind without considering surgical intervention. The operative risk, whether or not tabes or dementia paralytica complicates the picture, is considered less than that associated with the surgical treatment of a tumor.

*Orthostatic Circulatory Insufficiency in Tabes Dorsalis.*—Spingarn and Hitzig<sup>151</sup> call attention to the association of tabes dorsalis with orthostatic circulatory insufficiency. Three tabetic patients observed by them showed, in varying degrees, falling blood pressure, diminished venous return and impaired cerebral blood supply on the assumption of an erect position. Carotid sinus hypersensitivity was present in 2 of the patients. The recognition of such impaired orthostatic adjust-

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150. Schaub, C. F.: Surgical Treatment of Syphilitic Optic Atrophy (Syphilitic Optico-Chiasmatic Arachnoiditis), *Dis. Eye, Ear, Nose & Throat* 1:326 (Nov.) 1941.

151. Spingarn, C. L., and Hitzig, W. M.: Orthostatic Circulatory Insufficiency: Its Occurrence in Tabes Dorsalis and Addison's Disease, *Arch. Int. Med.* 69:23 (Jan.) 1942.

ment in patients with tabes may clarify the significance of vertigo and fainting of which tabetic patients may complain.

*Injury to the Intervertebral Disk from Lumbar Puncture.*—Munro and Harding<sup>152</sup> have demonstrated roentgenographically that perforating injury to the posterior portion of the annulus fibrosis is a distinct possibility during lumbar puncture whenever the needle penetrates too deeply. The authors recommend the abandonment of forced flexion of the spine and the use of the interspace between the last lumbar and the first sacral vertebra to decrease the possibility of this injury.

*Composition of Spinal Fluid Protein.*—The protein content of cerebrospinal fluid is of significance in the diagnosis of many neurologic disorders, including neurosyphilis. Little is known, however, about the origin or the composition of spinal fluid proteins or of the variations in composition which accompany disease states. Kabat, Landow and Moore,<sup>153</sup> who have used the Tiselius electrophoresis apparatus in the study of spinal fluid protein, note that the electrophoretic pattern of cerebrospinal fluid resembles that of blood plasma. Alterations in the composition of the serum proteins produce similar changes in the spinal fluid patterns. Colloidal gold activity with spinal fluid drawn from a person in a disease state is associated with the gamma globulin.

*Barrier Between the Blood and the Brain.*—Friedemann<sup>154</sup> has reviewed the facts relative to the blood-brain barrier which determines the distribution of substances between the blood and the central nervous system (as distinct from the barrier between the blood and the spinal fluid). This barrier is localized in the capillaries of the central nervous system which are endowed with selective permeability. The experimental evidence seems to indicate that the ability of substances to pass these capillaries is determined by their electrochemical properties. The cerebral capillaries are permeable to substances carrying a positive charge or no charge at the  $p_H$  of the blood, while they are impermeable to those carrying a negative charge. No attempt has yet been made to correlate the electrical charge of *S. pallida* with its ability to pass the capillaries of the central nervous system, although such a study would be of interest in connection with the much discussed problem of the existence of neurotropic strains of *S. pallida*.

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152. Munro, D., and Harding, W. D., II.: Lumbar Puncture: Its Potential Role in the Production of Injuries to the Intervertebral Disk, *J. A. M. A.* **119**: 482 (June 6) 1942.

153. Kabat, E. A.; Landow, H., and Moore, D. H.: Electrophoretic Patterns of Concentrated Cerebrospinal Fluid, *Proc. Soc. Exper. Biol. & Med.* **49**:260 (Feb.) 1942.

154. Friedemann, U.: Blood-Brain Barrier, *Physiol. Rev.* **22**:125 (April) 1942.

## SYPHILIS AND PREGNANCY

*Management.*—Howard<sup>155</sup> reviews the pathogenesis, diagnosis and management of syphilis in the pregnant woman. The duration of the infection in the mother and the treatment of the mother before and during pregnancy are considered the two major factors on which the health of the infant depends. Proper management requires follow-up examinations of the baby. The author believes:

The outlook for the control of congenital syphilis is encouraging in view of the rapidly declining incidence of early syphilis, improved treatment for syphilis both before and during pregnancy, and the better understood diagnostic criteria for the diagnosis of congenital syphilis. The routine blood testing of pregnant women should also be effective in preventing congenital infection. . . .

Benensohn<sup>156</sup> presents the results of therapy in 789 of 935 syphilitic pregnant women studied. The diagnosis of syphilis was based on the presence of a positive serologic reaction for syphilis, a history of early syphilis, previous stillbirths, premature labor, late abortions or positive serologic reactions for syphilis in the husband.

Routine treatment given to pregnant women in this clinic consists of concomitant weekly injections of 0.6 Gm. of neoarsphenamine and 0.13 Gm. of bismuth subsalicylate. The patients were divided into two groups based on the results of treatment, failure and "salvage." Failures included all patients aborting beyond the fourth month, those prematurely delivered of macerated or nonmacerated syphilitic fetuses, those delivered of stillborn fetuses or infants dying soon after birth and all infants who after birth presented evidence of congenital syphilis. The salvaged group included all infants followed for at least six weeks, during which time there was no evidence of congenital syphilis.

Of the 935 pregnant women studied, 789 were treated. For 54 of these, treatment resulted in failure. Therefore, 93.3 per cent of the infants were salvaged. Among 146 untreated patients, results in 58 (39 per cent) were considered failures. Better results are expected if patients receive more than ten treatments. However, a minimum amount of treatment was better than no treatment at all. The present series of patients was broken up into 608 patients who had not been previously treated and 327 who had received prior treatment. The results seem definitely better not only if the mother is treated with ten or more doses of an antisiphilitic compound during the course of pregnancy but if treatment has been given before pregnancy occurs.

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155. Howard, E. B.: The Significance of Syphilis in Pregnancy, *Ven. Dis. Inform.* **22**:387 (Nov.) 1941.

156. Benensohn, S. J.: Pregnancy in the Syphilitic Mother: A Study of Nine Hundred and Thirty-Five Pregnancies at the Cook County Hospital, *Am. J. Obst. & Gynec.* **43**:508 (March) 1942.



The incidence of congenitally syphilitic children is extremely high if secondary syphilitic lesions occur during pregnancy. In 9 patients with such lesions there were 5 in whom treatment failed. However, only 2 of the 5 patients received adequate therapy. Because of this high incidence of congenitally syphilitic children, resulting from a combination of pregnancy and early syphilis, 8 subsequent patients have been treated by means of the five day intensive therapy plan. The first of these had a primary lesion at term and was given forty-eight hours of continuous intravenous drip therapy, after which time she was delivered of a nonsyphilitic infant. The second had secondary syphilis at the eighth month of pregnancy and was treated intensively for five days, receiving 1,200 mg. of mapharsen. One month later she was delivered of a nonsyphilitic infant. Two additional patients gave birth to nonsyphilitic children; 1 patient aborted in the third month of pregnancy several days after completing her therapy. The other 3 patients were undelivered at the time this paper was published.

The data of Plass,<sup>157</sup> which detail the experiences of members of the department of obstetrics and gynecology of the State University of Iowa over a thirteen year period, indicate that the fate of the offspring of syphilitic women appears to depend less on the duration of the infection at the time of conception than on the extent of treatment during pregnancy. The best results were obtained when treatment during pregnancy followed anteconceptional therapy. In the author's opinion, unsupported by controlled observations, the pregnant woman with syphilis is "especially likely to develop treatment reactions to the arsenical antisymphilitic drugs."

Rolindo's<sup>158</sup> study of the placentas from syphilitic women shows that among those who were untreated for the disease there was more infiltration of the decidua basalis; greater hyperplasia of the villi, also with infiltration; more infarcts, and greater infiltration of the umbilical cord and the fetal membranes than among women who had received antisymphilitic treatment during pregnancy.

*Legal Aspects of Syphilis and Pregnancy.*—It has been more than twenty-five years since the first legal attempts were made to control the transmission of syphilis from one partner in marriage to the other. Peckham<sup>159</sup> summarizes the pros and cons of legislation relating to premarital and antepartum serologic tests. Emphasizing the efficacy of modern treatment in the prevention of congenital syphilis, the author expresses the belief that congenital infection will practically, if not

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157. Plass, E. D.: Syphilis in Obstetrics, *Am. J. Obst. & Gynec.* **43**:484 (March) 1942.

158. Rolindo, O.: Da influencia da sífilis na interrupção da prenhez, *Imprensa med.* **18**:87 (Dec.) 1941.

159. Peckham, C. H., Jr.: Legal and Therapeutic Aspects of Syphilis and Pregnancy, *J. A. M. A.* **117**:1863 (Nov. 29) 1941.

entirely, disappear as soon as all women consult their physicians early in pregnancy and the value of routine serologic tests and treatment becomes universally understood, and that legal requirement of premarital and antepartum serologic tests contributes to the eradication of syphilis.

*Administration of Clinics for Pregnant Women with Syphilis.*—Ingraham and Ingraham<sup>160</sup> indicate the need of special consideration for the pregnant woman with syphilis, both before and after delivery. From the administrative point of view the authors feel that congenital syphilis best can be prevented by the establishment of a special family clinic for the antepartum and postpartum treatment of the syphilitic pregnant woman and her newborn child. Such a clinic should be staffed by medical and attendance follow-up personnel with a special interest and training in control of syphilis. Facilitation of prompt and adequate treatment both for mother and for child is claimed for this administrative service.

#### CONGENITAL SYPHILIS

*Incidence.*—Wile and Mundt<sup>161</sup> have analyzed the records of 500 patients to determine the frequency of the various manifestations of untreated congenital syphilis and the combinations in which they occurred. Their patients were divided into an infantile and a tardive group, the former including patients up to the age of 2 years and the latter all others.

In the infantile group the authors made the following observations: 1. Except for four doubtful reactions the blood of all patients had strongly positive serologic reactions for syphilis. The reactions of the spinal fluid for syphilis were positive in 47 per cent of the 19 patients tested. 2. Involvement of the eyes and ears was uncommon. 3. Eighteen per cent had snuffles, a condition occurring three times as often in girls as in boys. 4. Twenty-seven per cent had cutaneous eruptions due to syphilis. Lesions of a mucous membrane were rare. 5. One third of the patients had a significant generalized lymphadenopathy. 6. Splenomegaly was present in 2 per cent of the group, and in 3 per cent both the liver and the spleen were enlarged. 7. Five per cent had active bone lesions and another 12 per cent inactive involvement of bone. Thirty-eight per cent of the patients presented developmental bone stigmas. 8. Of the 9 patients with neurosyphilis, one third were asymptomatic and one third had meningovascular syphilis.

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160. Ingraham, L. B., and Ingraham, N. R., Jr.: Prevention of Congenital Syphilis in Large Urban Hospital: Study of Clinic Administration, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:731 (Nov.) 1941.

161. Wile, U. J., and Mundt, L. K.: Congenital Syphilis: A Statistical Study with Special Regard to Sex Incidence, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:70 (Jan.) 1942.

The following observations were made on the tardive group:

1. Serologic reactions for syphilis were positive in 90 per cent. Twenty-seven per cent of 343 patients whose spinal fluid was tested had positive reactions for syphilis.
2. Eight per cent presented cutaneous changes, of which the most frequent was rhagades.
3. The most frequent abnormality of the nose and throat was saddle deformity, with an incidence of 10 per cent.
4. Deafness due to abnormality of the eighth nerve was reported in 6 per cent of the patients.
5. Fifty-nine per cent had ocular lesions. Interstitial keratitis, the most frequent manifestation of late congenital syphilis, occurred in 44 per cent of the patients, affecting females twice as often as males.
6. Thirty-one per cent of patients over the age of 6 had Hutchinson teeth, and in another 16 per cent the teeth were suggestively hutchinsonian.
7. Arthritis was an unusual finding. Clutton joints were reported in 2 per cent of the patients.
8. Hutchinson teeth were observed no more frequently in patients with interstitial keratitis than in those without. Deafness, however, occurred twice as often in association with interstitial keratitis as it did alone, and the same was true for Clutton joints. Hutchinson's triad occurred 9 times.
9. Serologic reactions for syphilis were positive in the same proportion in patients with and in those without interstitial keratitis. The spinal fluid gave a positive reaction for syphilis only half as frequently in patients with interstitial keratitis as in the entire group.
10. Bone lesions occurred in 39 per cent of the group.
11. In each type of clinical neurosyphilis males were affected more frequently than females. In 27 per cent of the group the spinal fluid gave a positive reaction for syphilis, and half of these patients were asymptomatic.

*Stigmas of Congenital Infection.*—Krantz<sup>162</sup> evaluates radial scars of the lips as a stigma of congenital syphilis. Other diseases, such as eczema, may produce these scars, but the author believes congenital syphilis to be the most frequent cause. The presence of radial scarring about the lips, especially when there is involvement of the vermilion border of the lips themselves or when the scarring is extensive, should always suggest the possibility of syphilitic infection.

Oldach<sup>163</sup> presents an evaluation of two physical signs considered by some to be stigmas of congenital syphilis. Among 92 patients with proved congenital infection, he encountered 5 with the swelling of the sternal end of either clavicle caused by syphilitic osteoperiostitis known as Higonmenakis's sign. Among the group were 3 patients with DuBois' sign, shortening of the fifth finger supposedly due to dys-

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162. Krantz, W.: Sind radiäre Lippennarben ein verlässliches Stigma der konnatalen Syphilis? *Dermat. Wchnschr.* **112**:369 (May) 1941.

163. Oldach, F. A.: Zur Bewertung des Klavikelsymptoms und des Kleinfingerzeichens bei der connatalen Lues, *Deutsche med. Wchnschr.* **67**:487 (May 2) 1941.

trophy of the middle phalanx. The latter sign, however, was also encountered 8 times in 123 nonsyphilitic persons, and the author does not regard it as a true stigma of congenital syphilis.

Fortes,<sup>164</sup> radiologist to the Hospital Jesús in Rio de Janeiro, surveys his experience with osseous syphilis in infants and children. In a profusely illustrated article he discusses syphilitic osteochondritis, osteoperiostitis and osteomyelitis and the differential diagnosis of rickets and scurvy.

*Dental Abnormalities Associated with Congenital Syphilis.*—De Alzaga and Sundblad<sup>165</sup> discuss the dental abnormalities encountered in 125 patients with congenital syphilis. Hutchinson incisors and agenesis of the lateral incisors are considered pathognomonic, but the cusp of Carabelli and the separation of upper central incisors (Gaucher's sign) are not. Retardation of the second dentition was no more frequent in persons with congenital syphilis than in normal subjects. Caries of the first molar was observed in 65 per cent of the patients with syphilis.

Attempting an analysis of the literature and of his own experience regarding congenital syphilis as an etiologic factor in malocclusion of the teeth, Stathers<sup>166</sup> finds that no particular type of malocclusion occurs with sufficient frequency to be considered characteristic.

According to Anderson,<sup>167</sup> in congenital syphilis there is a tendency toward a symmetric enamel defect characterized by thinning, pitting and grooving. The changes are similar to those due to rickets, although in syphilis the entire enamel is more likely to be involved.

*Syphilitic Aortitis in Congenital Syphilis.*—Yampolsky and Powel<sup>168</sup> have reviewed the literature on reported cases of syphilitic aortitis and aortic insufficiency in congenitally syphilitic children. They give a detailed report of a 9 year old Negress who came to the hospital complaining of shortness of breath, vomiting and pain in the stomach and the chest. The child's family history was negative except that at birth her mother was known to have had a positive serologic reaction for syphilis, and the cord and the sinus blood of the patient were also

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164. Fortes, J. F.: Lues óssea da primeira infância, Rev. méd. munic. **3**:7 (Jan.) 1942.

165. de Alzaga, S., and Sundblad, R. R.: Anomalías dentarias en la sífilis congénita, Semana méd. **49**:605 (March 26) 1942.

166. Stathers, F. R.: Congenital Syphilis and Malocclusions of the Teeth, Am. J. Orthodontics **28**:138 (March) 1942.

167. Anderson, B. G.: Developmental Enamel Defects, Am. J. Dis. Child. **63**:154 (Jan.) 1942.

168. Yampolsky, J., and Powel, C. C.: Syphilitic Aortitis of Congenital Origin in Young Children: Review of the Literature and Report of a Case, Am. J. Dis. Child. **63**:371 (Feb.) 1942.

reported as giving positive reactions for syphilis. The child had been quite well until the present illness and had not suffered from shortness of breath or pain in her joints. No stigmas of congenital syphilis were noted on physical examination. Attention was primarily directed to the heart; the rate was 136 per minute; there was a gallop rhythm, and a soft systolic murmur was heard at the apex. The heart was enlarged to the left and downward. Laboratory studies revealed leukocytosis and a positive serologic reaction for syphilis. Roentgen examination of the chest showed the heart to be enlarged in all diameters, but particularly was there enlargement of the left ventricle. An electrocardiogram showed a normal PR interval with slurring of the QRS complexes and a slight depression of the ST segments in leads I and II. The electrocardiogram was interpreted as showing myocardial disease. As a result of the clinical findings, the authors felt that it was only proper to make a diagnosis of congestive heart failure following rheumatic myocarditis with mitral valvulitis.

At necropsy the heart was carefully examined, and there was found no disease of the tricuspid, the mitral or the pulmonary valve. Except for slight widening of the commissures between the aortic cusps, the aortic valves were not remarkable. The intima of the aorta appeared edematous and lay in numerous longitudinal folds. This wrinkling and edema of the aorta were seen throughout the entire aortic arch. The microscopic appearance of the aorta was consistent with a diagnosis of syphilitic aortitis. Also observed was marked narrowing of the ostiums of the coronary arteries.

The authors believe that since there was no history or evidence of acquired syphilis on the external genitalia, this possibility must be excluded as a factor in the cause of death. The authors believe that the clinical and pathologic findings definitely point to the congenital origin of the aortitis.

*Interstitial Keratitis.*—Arena<sup>169</sup> reports the results of treatment of 7 patients with syphilitic interstitial keratitis with a sulfonamide compound. The purpose of the report is to stimulate interest in this type of therapy, so that further controlled studies will be made.

In this series all children had bilateral interstitial keratitis; only 1 had received previous antisyphilitic treatment. Five of the children received sulfanilamide; 1 received sulfapyridine (2-[paraaminobenzene-sulfonamido]-pyridine), and 1 received sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Along with this therapy antisyphilitic treatment was given. Photophobia and clouding of the cornea cleared up with remarkable rapidity within one to three weeks. It is felt that

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169. Arena, J. M.: The Use of Sulfonamides in the Treatment of Syphilitic Keratitis, *J. Pediat.* 20:421 (April) 1942.

this could only be due to the action of the sulfonamide compounds, since antisyphilitic therapy consisted of one or two doses of a preparation containing bismuth administered intramuscularly. No attempt has yet been made to apply the drugs locally. The author realizes that there is no evidence to substantiate the use of sulfonamide compounds in the treatment of this condition, since previous reports would indicate that they were not effective in the treatment of syphilitic infections.

*Congenital Syphilis in the Third Generation.*—Werner<sup>170</sup> has reviewed the literature pertaining to congenital syphilis in the third generation, adding 3 probable cases. Twenty-five of 47 cases culled from the literature are accepted as true infections in the third generation. In this group interstitial keratitis, Hutchinson teeth and tibial periostitis were the most frequent manifestations, with polar cataract, chorioretinitis and optic atrophy less frequently observed. Nonspecific dystrophies of one kind or another were noted in the majority of cases, and the author believes these stigmas merit special consideration.

#### SYPHILIS AND OTHER DISEASES

*Syphilis and Lymphogranuloma Venereum.*—In a study of the coexistence of lymphogranuloma venereum with other venereal diseases, Shaffer and his collaborators<sup>171</sup> studied 44 patients with syphilis. Of these patients, 30 white and 14 colored, 15 (34.1 per cent) had clinical evidence of lymphogranuloma venereum. The results of complement fixation tests for lymphogranuloma venereum were positive in 38 (86.4 per cent), and the results of Frei tests with chick embryo antigen (lygranum) were positive in 28 (63.6 per cent).

*Syphilis and Hypertension.*—Jacobs<sup>172</sup> discusses the management of the hypertensive patient with syphilis. In his opinion antisyphilitic treatment is contraindicated (1) when congestive heart failure is present or impending, (2) when the hypertension is severe (200 systolic and 120 diastolic), (3) when there has been recent coronary thrombosis or there are frequent attacks of angina pectoris considered not to be due to syphilitic aortitis, and (4) when the hypertensive patient is over 60 years of age.

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170. Werner, M.: Lues congenita in der dritten Generation. Ihre Symptomatologie und Bedeutung für die Klinik. Mitteilung von drei Fällen von Lues congenita der dritten Generation, Deutsches Arch. f. klin. Med. **187**:435, 1941.

171. Shaffer, M. F.; Rake, G.; Grace, A. W.; McKee, C. M., and Jones, H. P.: Lymphogranuloma Venereum Intercurrent with Other Venereal Diseases. Am. J. Syph., Gonorr. & Ven. Dis. **25**:699 (Nov.) 1941.

172. Jacobs, S.: Syphilis and Hypertension, Urol. & Cutan. Rev. **46**:241 (April) 1942.

Royster, Lisa and Carroll<sup>173</sup> analyze the postmortem observations on the hearts of 33 patients with cardiac failure occurring in association with combined hypertension and syphilis without aortic regurgitation. Hypertrophy tended to be extreme. Arteriosclerosis of the coronary arteries was notably more severe than that encountered in the hearts of patients in comparable age groups with hypertension not complicated by syphilis. Damage to the myocardium was extensive and attended by diverse pathologic processes, among which infection, both valvular and extracardiac, predominated. The authors note that the clinical course of their hypertensive patients with syphilis after cardiac failure supervened was strikingly similar to that of patients with syphilitic aortic regurgitation and failure.

*Syphilis and Rheumatic Heart Disease.*—Lisa, Solomon and Eckstein<sup>174</sup> report the anatomic observations in 14 cases of combined syphilitic aortic valvulitis and rheumatic heart disease. In 9 instances the aortic valve was affected by both a syphilitic and a rheumatic process. Syphilitic involvement of the coronary ostiums producing atresia or stenosis was noted 10 times. Rheumatic mitral valvulitis was present in all cases. Clinically, the course of the combined diseases tended to be progressive and the response to therapy poor. In the great majority of cases the patients died within one and a half years, many never having recovered from their first decompensation.

*Syphilis and Genital Lesions in the Female Due to Other Diseases.*—Speiser<sup>175</sup> says that infectious lesions about the external genital organs of the female offer a particularly intriguing problem, since the same etiologic factor may produce variable lesions and different etiologic factors may produce similar lesions. There may be a coexistence of several infectious lesions. The incidence of genital lesions per thousand women admitted to the gynecologic service of Bellevue Hospital, New York, is as follows: primary syphilis, 1.4; secondary syphilis, 0.9; lymphogranuloma venereum, 5.2; granuloma inguinale, 0.4; chancroid, 0.8; condyloma acuminata, 2.0, and abscess of Bartholin's glands, 30.6. It is pointed out that this is not the incidence of genital lesions among women admitted to the hospital as a whole. The characteristic lesions of gonorrhea, syphilis, chancroid, granuloma inguinale and lympho-

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173. Royster, C. L.; Lisa, J. R., and Carroll, J.: Anatomic Findings in the Heart in Combined Hypertension and Syphilis, *Arch. Path.* **32**:64 (July) 1941.

174. Lisa, J. R.; Solomon, C., and Eckstein, D.: The Heart in Combined Syphilitic Aortic Valvulitis and Rheumatic Heart Disease, *Arch. Path.* **33**:37 (Jan.) 1942.

175. Speiser, M. D.: Infectious Lesions About the External Genitals, with Special Emphasis upon the Diagnosis, *Am. J. Obst. & Gynec.* **43**:681 (April) 1942.

granuloma venereum are discussed. The common sites of chancre are given in their order of decreasing frequency as the fourchet, labia majora, labia minora, urethra, perineum, vagina, thigh and mons veneris. One must ever be mindful of the possibility of a syphilitic infection when lesions appear on the external female genitalia, since in the various localities there are great differences in the appearance of the primary lesion. For this reason, dark field examination should be made of material from all lesions on the female genitalia.

Under the discussion of chancroidal infections the author says that a diagnosis of chancroid should never be made without excluding syphilis because the lesions of the two diseases cannot be differentiated clinically. It is pointed out that the original soft chancre precedes the hard syphilitic one, because the incubation period of the former is much shorter. Suggestive characteristics of the superimposed hard chancre make themselves manifest only after the first few weeks of the chancroid.

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## Book Reviews

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**Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures.** By Wilder Penfield and Theodore C. Erickson, with special chapters by Herbert H. Jasper and M. R. Harrower-Erickson. Price, \$8. Pp. 623, with 163 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This comprehensive treatise on convulsive and allied disorders brings up to date existing knowledge on the subject and encompasses the authors' numerous contributions in the field. Dedicated to Hughlings Jackson and Charles Sherrington, the book effectively follows the former master in utilizing the phenomena of epilepsy in illuminating the details of cerebral function. It begins with a short history of epilepsy and continues with discussions of functional localization in the cerebral cortex; the mechanism of seizures; the types of lesions which may give rise to attacks; predisposition and inheritance; medical, symptomatic and surgical treatment, and methods of case analysis. Cranial roentgenology, including pneumography and arteriography, is described, and special chapters by the associate authors are included on electroencephalography and psychologic studies of patients with epileptic seizures. An extensive bibliography and an index add to the usefulness of the book.

There is no gainsaying that the book constitutes a definitive treatment of the subject. That its viewpoint is predominantly surgical is inevitable, considering the surgical interests of the authors, and perhaps can be excused, but it leads to a failure to give adequate consideration to the chemistry of the convulsive disorders, the role played by psychogenic factors in the precipitation of seizures and the place of psychotherapy in the management of patients with these disorders. Such defects militate somewhat against the usefulness of the book to general practitioners, who treat the great bulk of epileptic patients, but leave it valuable to specialists, who are more apt to encounter bizarre and exceptional types of symptomatic convulsions due to trauma and tumor.

Perhaps one should not quibble over matters of terminology. Despite general recognition of the disadvantages of the term "epilepsy," no suitable substitute has appeared. There must be a radical difference between patients who are subject to seizures throughout their whole lives without ever presenting evidence of structural disease of the brain and those who have attacks only because they have brain tumors. The authors use the term epilepsy to cover all conditions, and in the present state of knowledge (or ignorance) they may be justified. Yet in medical usage the word is coming more and more to be restricted to those conditions which are truly cryptogenic, and it seems scarcely right to speak of a patient as epileptic when he really suffers from cerebral tumor, eclampsia, Stokes-Adams syndrome or hypersensitivity of the carotid sinus reflex. The authors seem to be on even less defensible grounds when they classify as epilepsy the "dizziness," vertigo, facial and pharyngeal spasm and paresthesias, as well as the "threatend syncope," observed in cases of infratentorial tumor. Such symptoms, occurring in other pathologic conditions in the posterior fossa, do not strike me as epileptic. It would seem more reasonable to restrict the term epilepsy to truly cryptogenic fits and to describe similar, symptomatic phenomena as simply epileptoid.

Nevertheless the book is extremely valuable, particularly to neurosurgeons, as a compendium of knowledge on the subject and as a contribution to understanding of the functions of the cerebral cortex. The extensive chapter on electroencephalography is particularly worth while, although future work in the field may prove this modern method of study to be less final in the diagnosis of epilepsy than is often thought. On the whole, the book is so extensive, so inclusive in its

treatment of the many aspects of convulsive disorders and so exhaustive in its presentation of the authors' important work in the surgical therapy of focal seizures that no physician who would be well read can afford to neglect it.

**Paroxysmalnaya Tachycardia.** By Prof. M. E. Mandelstamm. Pp. 218, with 77 illustrations. Leningrad: Pediatric Medical Institute, 1940.

This volume presents a well organized collection of information on all types of paroxysmal tachycardia and other disturbances of the cardiac rhythm.

An extensive study of the subject has been carried on in Soviet Russia for the past ten or fifteen years, and this work points out the importance of a knowledge of disturbances of the cardiac rhythm and its relation to cardiovascular disease.

A short historical review is followed by chapters on pathologic anatomy, experimental data, etiology, pathology and clinical symptoms. Following this the different forms of graphic representation are described, including sphygmograms, phlebograms and electrocardiograms.

The author then mentions the clinical and the physical signs by which the different tachycardias may be suspected. He deals with paroxysmal fibrillation and flutter and other arrhythmias that occur in transitory stages. There is a chapter on terminology. About a quarter of the book is devoted to clinical course, progress and treatment.

The observations that are made are drawn from clinical cases encountered at the Institute.

As therapeutic measures the author describes mechanical agents and drugs. Among the mechanical agents pressure on the carotid sinus and on the eyeball proved most effective in arresting paroxysmal attacks.

The effect of drugs, such as digitalis, quinine, quinidine and mechohyl, which were successfully used in this study, is described in detail.

The importance of prophylactic measures is stressed as well. There is included a vast bibliography drawn from the Russian, English, French and German literature.

It is most gratifying to learn that studies of this type have now reached a high level in the Soviet Union. This study is well worth the consideration of any one interested in cardiac arrhythmias.

**Synopsis of Ano-Rectal Disease.** By Louis J. Hirschman, M.D., F.A.C.S. Second edition. Price, \$4.50. Pp. 315, with 182 text illustrations and 12 color plates. St. Louis: C. V. Mosby Company, 1942.

It is apparently the desire of the author to present a concise discussion of those diseases of the anus and rectum which are amenable to office treatment. Of necessity, discussion of major diseases of this region had to be omitted. Nevertheless wherever it is necessary, as in the discussion of a differential diagnosis, adequate reference to these conditions is made. Likewise, any discussion of pathologic aspects other than those referring to clinical findings was beyond the scope of this synopsis and consequently was not included.

In limiting the major part of the discussion to the commoner diseases of the anus and rectum, the author has been able to present his subject in considerably more detail than would have been otherwise possible in a synopsis. The symptomatology, as well as the gross pathologic changes encountered in various diseases, is clearly and adequately discussed. The pitfalls and difficulties encountered in treating these diseases are stressed in the description of the choice of therapy. Some of the therapeutic procedures presented as being tractable to an office practice may seem a little ambitious for an average physician's office. However, the author discusses the necessary equipment, as well as emphasizes the importance of having it, if such procedures are to be performed under office conditions. Wherever necessary, adequate illustrations are inserted. These augment the descriptions to which they refer and add much to the simplicity of the presentation.

Students, as well as "general surgeons," should find this book of value. To students it will serve as an excellent introduction to a more detailed discussion

of the diseases of the anus and rectum. A "general surgeon" whose practice includes the treatment of these conditions will find the discussions of differential diagnosis, as well as the presentation of therapeutic procedures, of value.

**The Complete Weight Reducer.** By C. J. Gerling. Price, \$3. Pp. 246. New York: Harvest House,

This handbook on weight reduction, written for the layman, has been arranged in the form of a dictionary with brief paragraphs devoted to various aspects of the subject. The items discussed are arranged in alphabetic order. For example, on one page the following headings are found: "Cream (dairy)," "Creams for Reducing," "Cure of Obesity," "Cushing's Syndrome" and "Cycling"; on another, "Perspiration in Reducing," "Perspirator," "Petersime Electro-Thermo Bath," "Phenolphthalein" and "Phosphorus." From the brief and often inadequate discussions devoted to each subject a few isolated facts may be learned, but there is no continuity of thought. Subjects discussed include food values, sample diets and menus, exercise for reducing, metabolism, endocrine glands, quackery and fraud.

The author suggests in the introduction that the arrangement of the book permits the reader to "go immediately to any feature or aspect of the whole problem of reducing as it exists today and there find adequate information without working his way through a mass of data that is at the moment of no interest to him."

In the opinion of the reviewer, this encyclopedic method of presentation destroys any value which the subject matter presented might otherwise have.

**Occupational Diseases: Diagnosis, Medicolegal Aspects, and Treatment.**

By Rutherford T. Johnstone, M.D. Price, \$9. Pp. 558, with illustrations. Philadelphia: W. B. Saunders Company, 1941.

The author has gleaned from twenty-five years' experience in a surgical and medical industrial service, with admissions exceeding 11,000 patients per year, a practical groundwork for a discussion of various occupational diseases. The patients admitted represented such diverse sources as chemical, mechanical, general manufacturing industries, agriculture, cattle raising, meat packing, fishing, canning, shipbuilding and airplane construction. Since patients were, to a large extent, referred by physicians in a number of localities, with a previous estimate of their condition and medicolegal status, the author has had an opportunity to obtain a cross section of the existing viewpoint among industrial physicians and general practitioners with regard to the purpose of compensation, as well as a chance to note the phases of industrial medicine not understood by members of the medical profession at large. For example, he states he is impressed with the fact that a scientific basis for diagnosis of the more frequent occupational diseases is not adhered to by the majority of physicians.

Such experiences have helped the author to present his subject with emphasis on the practical needs of practitioners.

**Occupational Tumors and Allied Diseases.** By W. C. Hueper. Price, \$8.

Pp. 896. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

On opening this imposing volume one wonders how there is enough material on the occupational aspect of tumors to fill it, but in actual fact there is little overlap with what one finds in the usual textbooks on tumors. Nearly 300 pages are devoted to tumors of the skin, and this section contains a mine of useful material. Under the heading Occupational Tumors of the Respiratory System one finds, in addition to statistical discussions on the increase of tumors of the lung, discussions of such matters as the influence of silica, asbestos, iron, arsenic, chromates, nickel carbonyl, gases and fumes, tar, pitch, liquid petrolatum, paraffin, soot and radioactive agents. Other sections are treated with similar thoroughness, and the whole book contains an invaluable mass of material for reference. There is a thorough bibliography.

# ARCHIVES of INTERNAL MEDICINE

VOLUME 70

DECEMBER 1942

NUMBER 6

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## POLYCYTHAEMIA VERA

REPORT OF A CASE

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In May 1783, when Harvard Medical School was in its infancy, Dr. Benjamin Waterhouse presented a paper before the American Academy of Arts and Sciences. This was the first communication to any scientific body from a member of the faculty of Harvard Medical School and therefore may be regarded as an important foundation stone on which have been superimposed all subsequent medical publications by graduates of this school. At that time he said in nearly these words:

I appeal to every practitioner who like me has anxiously turned over the observations of others in hopes of finding something to guide him in a case which puzzles him to commit to writing the observations which he makes in order that an exact account of a hitherto inexplicable disorder may be transmitted to his successors.

With this precept in mind the following account of a case of polycythaemia vera is recorded. The case appears unusual in that so far as can be determined it is the first example of the disease to be described in which the clinical picture of polycythaemia vera was seen to develop in a person previously regarded as normal, in which its clinical earmarks disappeared under treatment and in which, finally, it left behind a variety of interesting vestiges of its previous existence.

### REPORT OF CASE

In 1930 H. S., a 50 year old physician of Yankee breeding, presented himself for physical examination. He was a hard working practitioner, was well so far as he knew and had been free of any serious illness in the past beyond an attack of pneumonia ten years before. His only complaint was that for many years he had suffered from attacks of migraine, never producing sufficiently bad headaches to interfere with his work but of late becoming more frequent and being accompanied by nausea and vomiting.

The results of his general physical examination were unremarkable. The blood pressure was 140 mm. systolic and 80 mm. diastolic. Retinal examination revealed well outlined disk margins and normal-appearing vessels. The peripheral vessels seemed normal. The urine was free of albumin and sugar and contained an occasional leukocyte in the sediment. The hemoglobin concentration was 90 per cent. The red and the white cells were normal in appearance. The Wassermann reaction was negative.

The patient felt well for the next four years. Then he returned for rechecking. He had gained 14 pounds (6.5 Kg.) in the interval. He was a little concerned, he said, because his blood pressure was "climbing up," and because recently when he examined his own urine, he found that it contained "plenty of albumin and casts."

During the past four years his headaches had decreased in intensity. He remarked that he believed his peripheral vessels were becoming tortuous and sclerosed, and he feared that he was becoming generally arteriosclerotic, because he seemed to tire out more easily on less work and in general to feel less energetic than he would like. But on the whole he had no striking complaints.

His appearance was about as it had been except that he now appeared rather flushed and had a suggestion of puffiness around the eyes. The heart was not hypertrophied, and the eyegrounds failed to show any obvious vascular lesions. The blood pressure was 160 mm. systolic and 80 mm. diastolic. The peripheral vessels were, in fact, palpable, though it was difficult to measure how much they had changed since the first observation. The spleen was not felt. A specimen of urine excreted during the day contained 350 mg. of albumin per liter, while a sample of urine excreted during the night was albumin free. Neither specimen contained sugar or casts. The concentration of nonprotein nitrogen in the blood was 34 mg. per hundred cubic centimeters. Unfortunately, no blood counts were made.

In 1935, a year and a half later, he appeared for the third time. He had lost 11 pounds (5 Kg.) in weight since his last visit for no reason that he knew. He was convinced that his systolic blood pressure now was in the neighborhood of 180 mm. most of the time. More particularly, however, he had begun gradually to experience persistent and disabling headaches, not of the migrainous type but more continuous, often waking him up at night and lasting for two or three days. Along with this he noticed that his memory was failing, that his face flushed easily and often looked so red as to make him feel self conscious and that he had reddish blue hands and feet, which were often painful, characteristic, in his opinion, of erythromelalgia.

On physical examination his face was flushed and bluish red. The eyegrounds did not show any especially noticeable vascular lesions, but the veins were overfull and distended. The heart was normal, although, as the patient had observed, the systolic blood pressure was 180 mm. The spleen was enlarged, so that its edge was easily felt. The urine contained 4.0 Gm. of albumin per liter and contained in the sediment many hyaline casts and a few leukocytes. The hemoglobin concentration was 145 per cent, and the red cell count was 8,800,000. The hematocrit reading showed that nearly 80 per cent of the volume of the blood was corpuscular.

*Comment.*—In this fashion the polycythemia became apparent, so insidiously as to make its exact mode of onset uncertain and so gradually as to make it impossible to say in retrospect whether it commenced one, three or five years before it was recognized. Because arterio-

sclerotic changes in the peripheral vessels and hypertension also had advanced in the same insidious fashion during observation, one could not help but wonder whether whatever caused the vascular disease, on the one hand, had not caused the polycythemia, on the other, or whether the clinical blossoming of polycythemia was not, in fact, a local manifestation of a general vascular disorder.

Even a single case in which polycythemia is seen to develop as it did in this one disposes whoever observes the phenomenon to place a good deal of weight on the studies of Reznikoff, Foot and Bethea.<sup>1</sup> They claimed that if the bone marrow of a patient with polycythemia is studied by appropriate staining methods there often can be demonstrated in it such vascular changes as thickening of its capillary walls and subintimal or adventitial fibrosis of its arteries and arterioles, a state of affairs well able to produce chronic anoxemia of the bone marrow and resultant polycythemia. Some such lesion as this, it seemed, might well have developed in our case.

In any event a definite diagnosis was established, and the question of treatment arose. The most appropriate management of polycythemia is somewhat confusing to select; any practitioner who turns to the observations of other investigators on this point, in hopes of finding something to guide him in a case which puzzles him, will discover that opinions nowadays differ and perhaps are recorded by personal friends, so that unbiased judgment may be difficult. Our fellow Bostonian, Dr. Joseph H. Pratt, and his associate Morawitz<sup>2</sup> deserve credit for suggesting in 1908 that phenylhydrazine might be a useful drug to administer when destruction of blood is desirable. No one who has visited the Mayo Clinic can help but be impressed by the results obtained there with phenylhydrazine in the treatment of polycythemia, as reported by Giffin and his associates.<sup>3</sup> On the other hand, there are other methods which have been used with equal success. For many years Haden,<sup>4</sup> of the Crile Clinic, Cleveland, has upheld stoutly that intelligent venesection, with due attention to the total blood volume, is the therapeutic method of choice. Irradiation with roentgen rays

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1. Reznikoff, P.; Foot, N. C., and Bethea, J. M.: Etiologic and Pathologic Factors in Polycythemia Vera, *Am. J. M. Sc.* **189**:753-759 (June) 1935.

2. Morawitz, P., and Pratt, J.: Einige Beobachtungen bei experimentellen Anämien, *München. med. Wchnschr.* **55**:1817-1819 (Sept. 1) 1908.

3. Brown, G. E., and Giffin, H. Z.: The Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine, *Arch. Int. Med.* **38**:321-345 (Sept.) 1926. Giffin, H. Z., and Allen, E. V.: The Control and Complete Remission of Polycythemia Vera Following the Prolonged Administration of Phenylhydrazine Hydrochloride, *Am. J. M. Sc.* **185**:1-12 (Jan.) 1933.

4. Haden, R. L.: The Red Cell Mass in Polycythemia in Relation to Diagnosis and Treatment, *Am. J. M. Sc.* **196**:493-502 (Oct.) 1938.

or radioactive phosphorus, as demonstrated recently by Lawrence,<sup>5</sup> can be useful, or if one is more conservative, arsenic in the form of solution of potassium arsenite U. S. P. (Fowler's solution), as employed by Forkner, Scott and Wu,<sup>6</sup> may be of measurable service. Proper regulation of diet, it is almost generally agreed, must always be advised, as the value of a low iron diet has been repeatedly emphasized. Dameshek and Henstell<sup>7</sup> have described the details of a practical diet for the treatment of polycythemia.

On the whole, in reviewing the experience of other investigators in the treatment of polycythemia it was fairly evident that a diet low in iron combined in some fashion with solution of potassium arsenite, bleeding, administration of phenylhydrazine or irradiation were the four most popular methods of treatment then in vogue, each having respectable proponents and opponents. To our way of thinking at the time, phenylhydrazine had certain disadvantages, as emphasized by Giffin and Conner<sup>8</sup>; all were particularly noteworthy for our patient, since one of us (R. F.) had lately encountered an elderly patient with marked arteriosclerosis who was unduly sensitive to the drug and in whom nearly fatal hemolytic anemia, complicated by thrombosis of the splenic vein, developed after phenylhydrazine therapy.

The bleeding technic, as outlined by Haden, seemed simple and rational enough, but the patient himself voted against it. He was familiar with two pieces of work which had been talked of in Boston and which had impressed his mind: one by Forkner and his colleagues, on the beneficial use of solution of potassium arsenite in the treatment of certain patients with polycythemia, and the other by Minot and Buckman,<sup>9</sup> who described 3 patients who had been polycythemic for several years and in whom a profound degree of anemia eventually developed. He said if there was any possibility of his having a disease which began with polycythemia and ended with anemia, his own blood might some day be useful to him and he would like to keep it for a while. He preferred at first to follow a therapeutic program which was as harmless as possible and yet at the same time was based on sound principles. To his way of thinking clinical trial for

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5. Lawrence, J. H.: Nuclear Physics and Therapy: Preliminary Report on a New Method for the Treatment of Leukemia and Polycythemia, *Radiology* **35**:51-60 (July) 1940.

6. Forkner, C. E.; Scott, T. F. M., and Wu, S. C.: Treatment of Polycythemia Vera (Erythremia) with Solution of Potassium Arsenite, *Arch. Int. Med.* **51**:616-629 (April) 1933.

7. Dameshek, W., and Henstell, H. H.: Diagnosis of Polycythemia, *Ann. Int. Med.* **13**:1360-1387 (Feb.) 1940.

8. Giffin, H. Z., and Conner, H. M.: The Untoward Effects of Treatment by Phenylhydrazine Hydrochloride, *J. A. M. A.* **92**:1505-1507 (May 4) 1929.

9. Minot, G. R., and Buckman, T. E.: Erythremia (Polycythemia Rubra Vera), *Am. J. M. Sc.* **166**:467-489 (May) 1923.

a reasonable length of time of a compound containing arsenic supplemented by a low iron diet seemed most satisfactory. Accordingly, he began to diet and to take solution of potassium arsenite U. S. P. (Fowler's solution).

The effect of this part of his treatment is difficult to evaluate. It appeared to be partially effective but was by no means entirely successful.

Apparently the solution of potassium arsenite brought about a slight fall in hemoglobin, red cell count and hematocrit reading. Perhaps the spleen grew a little smaller. There was no significant change in the level of body weight or blood pressure. The patient felt better, but on the other hand, he began having attacks of angina pectoris, which worried him, and he had an attack of herpes zoster, followed

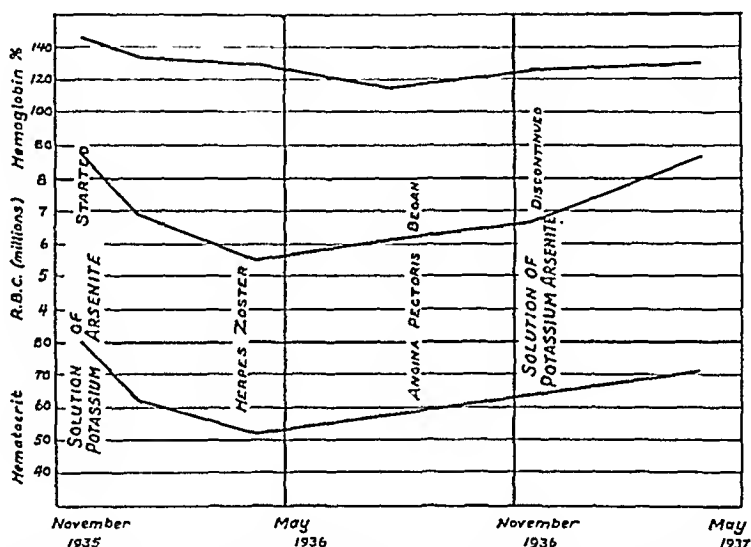


Fig. 1.—Effect of solution of potassium arsenite on the blood of a patient with polycythaemia vera.

later, after therapy with solution of potassium arsenite had been stopped and then reinstated, by a dark-looking skin and a certain amount of chronic indigestion. Having taken potassium arsenite for a year, with only the improvements just mentioned, he rested for four months from all treatment other than diet and at the end of March 1937 declared himself ready to try another therapeutic approach.

In June 1936 there had been published in the *New England Journal of Medicine* a paper by Hunter,<sup>10</sup> of the Massachusetts General Hospital, which attracted considerable attention locally. This dealt with "spray" radiation therapy and included reports of 2 cases in which Hunter had used this method in treating patients with polycythemia and had followed them carefully for three years afterward. The results which were obtained seemed promising. The patient knew of this

10. Hunter, F. T.: "Spray X-Ray Therapy" in Polycythemia Vera and in Erythroblastic Anemia, *New England J. Med.* **214**:1123-1127 (June 4) 1936.



paper; he admired Dr. George W. Holmes and the Massachusetts General Hospital, and he therefore decided on a course of roentgen therapy under the hands of that roentgenologist at that institution. He received seven treatments between April 3 and 12, 1937 in daily doses of 70 r and five treatments beginning May 4 and ending May 8 in daily doses of 70 r. Thus, he received a total dose of 840 r. The rays were sprayed on the anterior and the posterior surface of the body on alternating days over an area which included the entire trunk, the lower part of the neck and both femoral regions. Dr. Holmes informed us that the exposure time at each treatment was twenty minutes and that other factors in the procedure were as follows: The roentgen rays were produced by a current with 200 kilovolts. The rays were filtered through 0.5 mm. of copper and 4.0 mm. of aluminum. The target-skin distance was 175 cm.

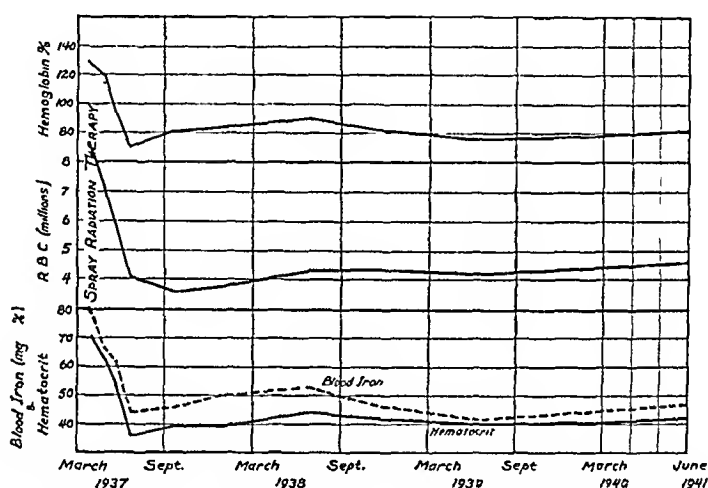


Fig. 2.—Effect of spray radiation on the blood of a patient with polycythemia vera.

The result of this treatment was gratifying. So far as one could measure clinically, the polycythemia disappeared.

The blood count returned to normal in every way and remained normal or even subnormal for the rest of the patient's life. His general condition improved remarkably. He gained 16 pounds (7.3 Kg.) in weight, carried on a heavy practice without complaint, felt normally well and claimed that his only physical limitation was due to what he termed "that damned angina."

*Further Details of Case.*—Clearly, in reexamining the patient from time to time, it was evident that his vascular disease progressed. Each time the blood pressure was estimated, the level was far too high. He came to have a great deal of angina, relieved in part by the steady use of theophylline with ethylenediamine and glyceryl trinitrate. He had one major attack which was suggestive of coronary thrombosis. He quickly grew to look older, as do so many people with advancing vascular disease. He had one minor attack of transitory aphasia,

which made him regard his cerebral vessels with distrust. Yet on the other side of the picture, he was able to do a man's work each day; the overfull veins of the eyegrounds disappeared; the size of the spleen receded, so that it became impalpable; his headache and mental stuffiness disappeared, as did the pain in his arms and legs, and whatever signs of renal involvement there ever were, vanished. The concentration of nonprotein nitrogen in the blood remained low, and the urine never showed more than the faintest trace of albumin, with normal sediment.

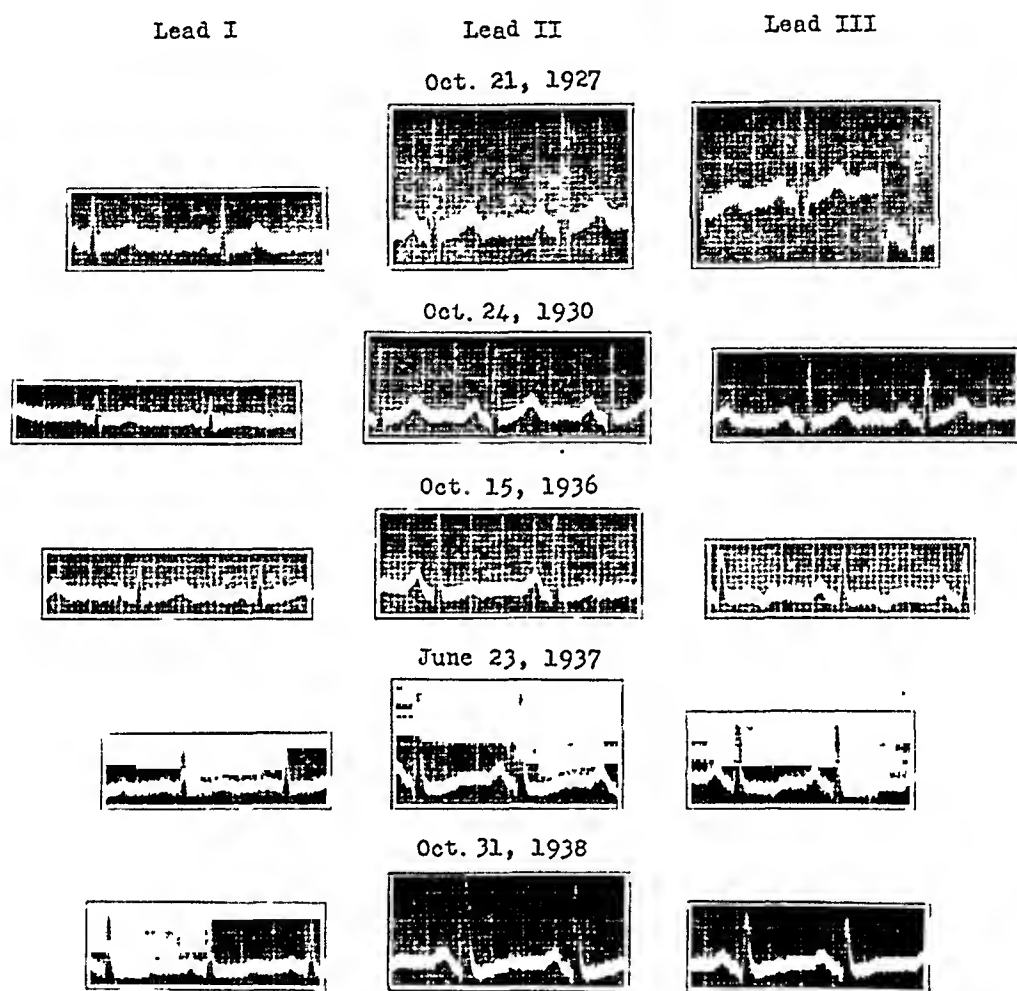


Fig. 3.—The progress of vascular disease in a patient with polycythemia vera, as shown by serial electrocardiographic tracings. There is a gradual and progressive change in the form of the ventricular complex in all three leads.

(This comment was provided by Dr. S. A. Levine, who made the tracings.)

The patient died in his office suddenly in November 1941, four and a half years after his course of roentgen treatment was completed and just as he had finished a busy afternoon of seeing patients.

Necropsy: Macroscopic examination. The heart was slightly hypertrophied. There were two small areas of dense gray fibrous tissue apparently from old infarctions, one approximately 5 mm. in diameter near the apex of the left ventricle in the outer wall, the other about 1 cm. in diameter in the interventricular septum just beneath the mesial cusp of the aortic valve. No recent infarcts were seen. The appearance of the heart muscle was more normal than would have been expected from the condition of the coronary vessels. The

endocardium was normal except for atheromatous thickening, with some calcification of the mitral and the aortic valve base.

Both coronary vessels showed an advanced degree of atheromatous degeneration, with many calcified plaques appearing in beadlike chains along the surface vessels. The right coronary artery, beginning 1 cm. distal to its orifice, was a solid fibrous cord, with only a threadlike lumen no more than 0.25 mm. in diameter.

The aorta showed advanced arteriosclerosis throughout its entire course. This was most pronounced below the diaphragm, the abdominal aorta having several extensive atheromatous ulcers and plaques of calcification. There was no thrombosis.

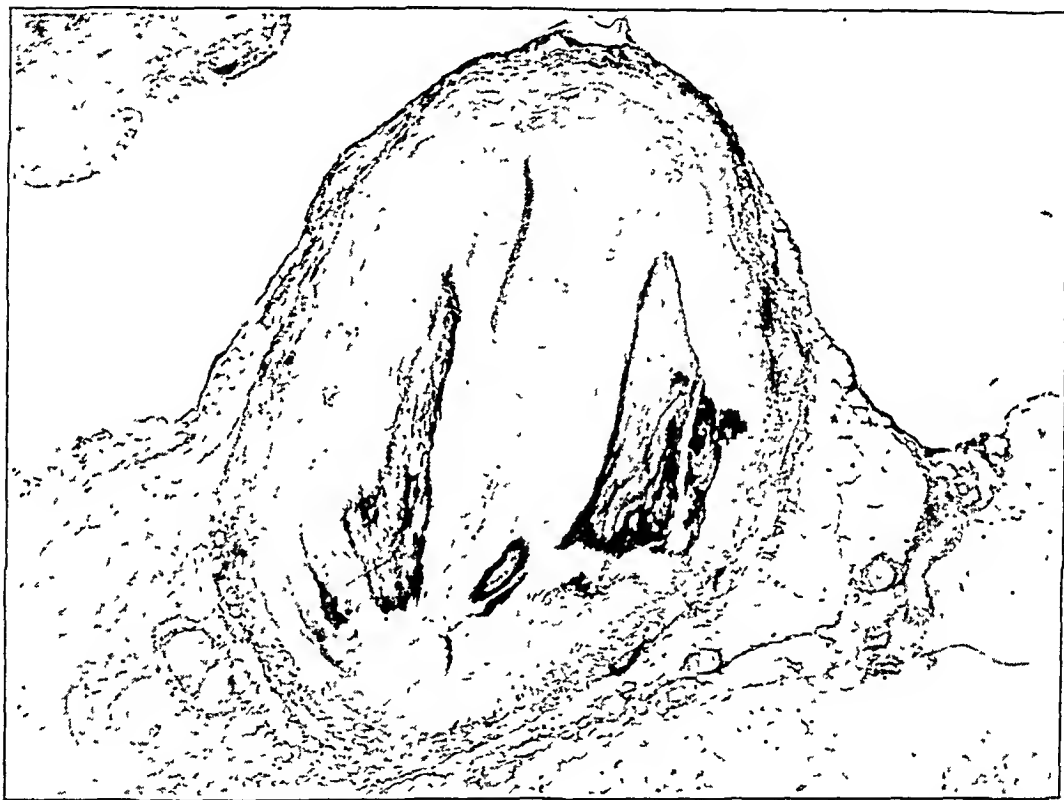


Fig. 4.—The right coronary artery ( $\times 30$ ). A section through its middle portion, showing complete occlusion by an old, organized thrombotic mass. There is partial calcification of the artery and no canalization of any consequence.

The vessels of the lung showed only a minimal degree of atheromatous change, and the lung tissue itself had no chronic inflammatory process, so that nothing like Ayerza's disease could account for the polycythemia. The mediastinum also was normal.

The liver was congested but otherwise showed no abnormality on gross examination.

The spleen was about twice normal size. The splenic artery was markedly sclerosed and contained many atheromatous plaques. In fact, the lumen of the vessel appeared to be only about half the normal diameter. The gross appearance of the spleen was that of congestion, although the capsule was flecked with

many minute siderotic nodules, such as frequently are seen in association with Banti's syndrome.

The kidneys were of about normal size and shape. The renal arteries presented an advanced degree of atherosclerosis, in many areas so marked as almost completely to occlude the vessels. On the other hand, the normal relation between cortex and pyramids was well preserved.

The cortex showed no gross abnormalities; the capsule stripped easily, leaving a uniformly granular surface, and the pelves and ureters were normal. The disparity between the amount of atherosclerosis in the renal arteries and the relatively normal appearance of the renal tissue was striking.

The gastrointestinal tract and the pancreas were not noteworthy.

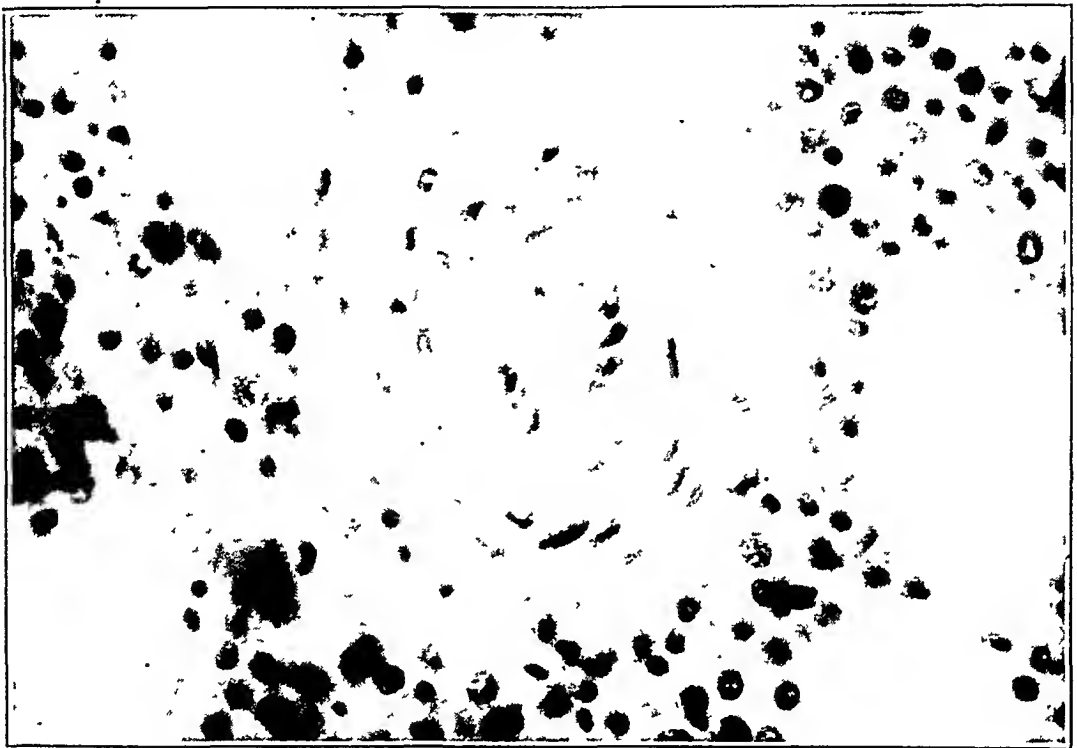


Fig. 5.—Vertebral marrow ( $\times 400$ ). The arteriole shown in the center is practically occluded by fibrous thickening of the media. There is marked erythroblastosis.

The sternal, vertebral and femoral bone marrow appeared normal. The femoral marrow was bright lemon yellow, fatty and did not show any recognizable islands of secondary hyperplasia.

Microscopic examination. There were striking vascular changes in all the tissues examined, particularly noteworthy in the vertebral and sternal bone marrow, the spleen, the kidney and the heart.

Through various portions of the heart advanced myocardial fibrosis was apparent. There were extensive areas in which muscle bundles had disappeared entirely and were replaced by a relative increase of the connective tissue about them. The majority of the blood vessels showed well defined fibrous thickening of the intima, and the right coronary artery and its branches were completely occluded by masses of dense, old, organized thrombotic material.

The kidneys also showed changes of vascular origin. There were areas in which the glomeruli were sclerosed, in which the tubules were atrophic or absent and in which the connective tissue was relatively increased and infiltrated with lymphocytes. The majority of the afferent arterioles were almost totally occluded by dense patches of hyalinization, in places having the appearance of necrotizing arteriolitis.

The germinal centers of the spleen were well preserved and stood out sharply but on close examination were definitely hematopoietic. Through the stroma was a moderate degree of general fibrosis, but in addition there were scattered small areas of active hematopoiesis in which both erythrocytic and leukocytic elements were present

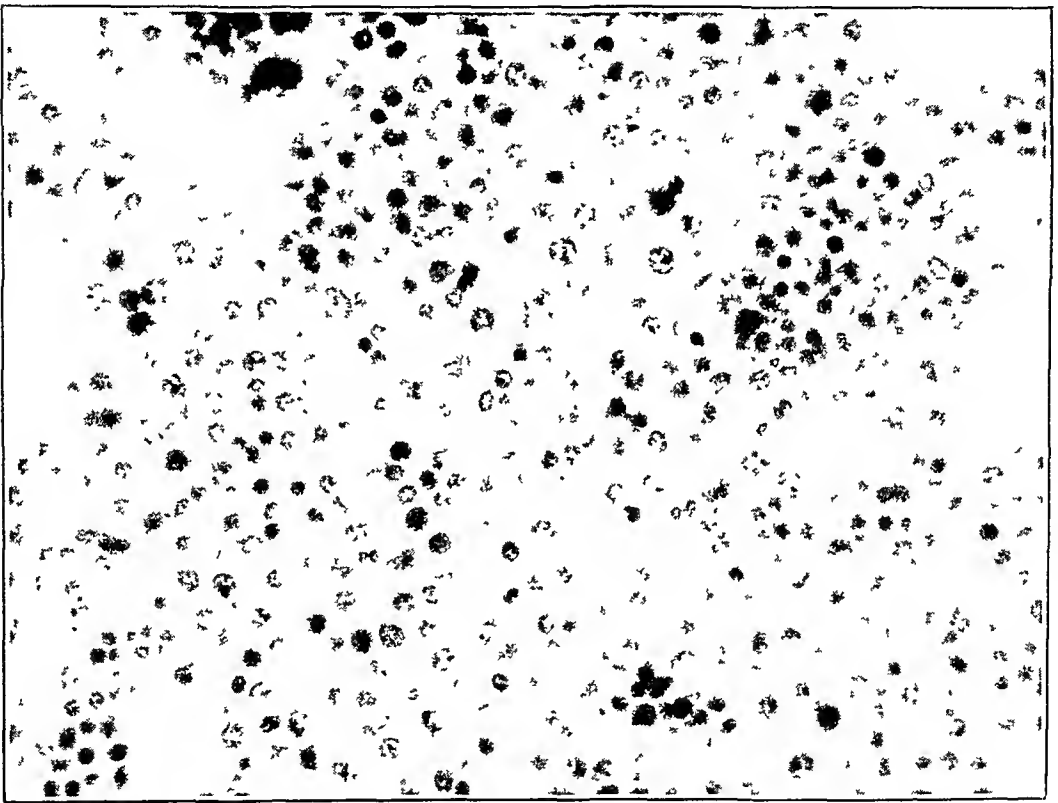


Fig. 6.—Sternal marrow ( $\times 375$ ). There is marked erythropoiesis.

The capsule was thickened, and in it were large numbers of hemosiderin-laden macrophages and of infiltrating lymphocytes and endothelial cells. Scattered throughout were many minute petechial hemorrhages.

The splenic arterioles tended to be fibrosed, with hyaline thickening of the intima. This change, however, was no more marked than often occurs in elderly persons with arteriosclerosis.

The bone marrow was especially interesting. The femoral marrow was not remarkable. Sections through the vertebral and the sternal marrow, however, revealed essentially the same picture. There was active erythropoiesis, not accompanied by a concomitant degree of new white cell formation. A moderate number of fat cells were present, and relatively large numbers of megakaryocytes

were visible. The arterioles and the capillaries presented well defined and unmistakable fibrous thickening.

The lungs were not remarkable except that many of the peribronchial arterioles showed fibrous thickening of the intima, often involving the inner portion of the media. The liver did not present any striking histologic abnormalities. The vessels of the adrenal glands were also involved in the general picture of vascular disease which was present; several of the smaller arterioles were occluded by atheromatous plaques with fibrosis and hyalinization of the intima and the media. Naturally, sections from the aorta showed extensive subintimal patches of atheromatous degeneration infiltrated with many fat-laden macrophages, lymphocytes and neutrophils.

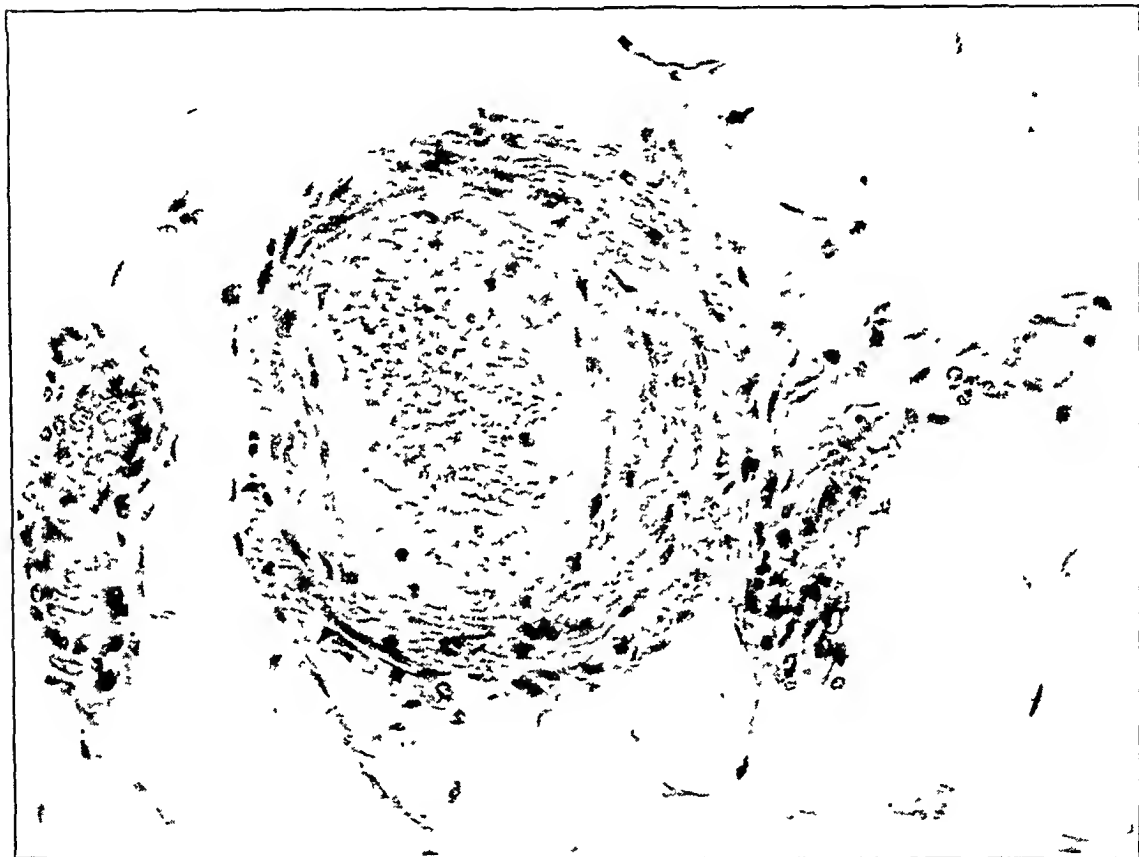


Fig. 7.—Femoral marrow ( $\times 150$ ). Section through the middle portion of the femur. There is no evidence of erythropoiesis, as appeared in the sternal and the vertebral marrow. The wall of the arteriole shown in the center is thickened because of fibrosis.

#### COMMENT

One phase of polycythaemia vera has received but little study; this concerns iron. Obviously, the vast number of red cells and the high concentration of hemoglobin utilize a great deal of this element. It has been assumed that this is obtained from deposits in the body. When our patient was polycythemic, a good share of his stored iron must have been in circulation, hence we were curious to ascertain what effect, if any, this had on the final iron content of his tissues.

Comparatively little has been acquired during the past thirty years in the way of authentic record of the iron content of human tissues. Magnus-Levy<sup>11</sup> in 1910 analyzed one body from this viewpoint; van Itallie in 1926, as reported by Donath,<sup>12</sup> and Donath himself in that year made more extensive analyses; in 1930 Horsters<sup>13</sup> became interested in the iron content of the organs in different forms of jaundice, reporting at the same time a few control figures from patients without jaundice, and in 1935 Sheldon,<sup>14</sup> in his excellent monograph on hemochromatosis, gave figures for the iron content of tissues of patients dying of this disease, appending to his tables a contrasting series of "normal control figures." These are all the available data that we could find.

There is general agreement that kidney, liver, spleen and striated muscle are the most important storehouses in which hoarding or depletion of iron becomes evident. The following tabulation is of some interest:

	Kidney	Liver	Spleen	Striated Muscle
Iron in Mg. per Cent of Dried Tissue				
Magnus-Levy, 1910, normal subjects.....	83	335	386	125
Horsters, 1930, "control cases".....	97	345	404	...
Sheldon, 1935, "normal control figures".....	39	50 to 100	140	25
Our patient .....	49	153	136	41
Iron in Mg. per Cent of Undried Tissue				
Donath, 1926, Chinese and native Dutch East				
Indians .....	11	21	48	...
van Itallie, 1926, European subjects.....	6	18	51	...
Our patient .....	8	42	30	...

There is a wide discrepancy in these figures. Ours are considerably lower than the ones reported by Magnus-Levy or Horsters but agree fairly well with those of Sheldon, Donath and van Itallie except as they concern liver. Our figures are directly comparable with Sheldon's, for like him we employed the technic of ashing and the method of Kennedy<sup>15</sup> for analysis for iron.

11. Magnus-Levy, A.: Ueber den Gehalt normaler menschlicher Organe an Chlor, Calcium, Magnesium und Eisen sowie an Wasser, Eiweiss und Fett, *Biochem. Ztschr.* **24**:362-380, 1910.

12. Donath, W. F.: Chemical Iron Analysis in Organs, *Mededeel. v. d. dienst d. Volksgezondh. in Nederl.-Indië* **3**:184-239, 1926.

13. Horsters, H.: Ueber den Eisengehalt der Organe beim Ikterus, *Arch. f. exper. Path. u. Pharmacol.* **152**:198-209, 1930.

14. Sheldon, J. H.: *Haemochromatosis*, London, Oxford University Press, 1935, pp. 205-219.

15. Kennedy, R. P.: The Quantitative Determination of Iron in Tissues, *J. Biol. Chem.* **74**:385-391 (Aug.) 1927.

Sheldon said of liver :

The normal standard is somewhat variable, but the average normal dry percentage is usually between 0.05 per cent. and 0.1 per cent., which implies an increase in haemochromatosis of some 40 times the normal.

One may conclude, therefore, that the liver iron of our patient may have been higher than normal, perhaps from chronic passive congestion, but it was by no means strikingly so. Otherwise, there was nothing in our data to suggest that excess storage of iron in any ordinary area or unusual withdrawal of iron from it played any part in the clinical picture which we observed.

This case raises three interesting questions: Why did the patient become polycythemic? What was the exact effect of the irradiation? Why did he have so long a remission?

As has been mentioned, the thought that vascular disease was the underlying lesion in this instance has considerable appeal. It is easy to imagine that vascular disease, when so general as it was here and involving as it did small vessels of the bone marrow, might cause thereby a chronic anoxemia of the red cell-forming apparatus. A few years ago Monge<sup>16</sup> pointed out the great similarity between the erythremic type of high altitude disease and polycythaemia vera, the chief difference being that erythremia due to high altitude subsides promptly when the patient lives at sea level. As a theory to explain the course of our patient's illness one might postulate a vascular lesion with involvement of the bone marrow circulation which made the blood behave as though the patient, to all intents and purposes, were living at a high altitude. As the blood count fell to normal, the blood lost its excessive viscosity; the circulation in the marrow improved; perhaps a new and effective capillary circulation was able to develop to a certain extent; the patient came back to earth, so to speak, and the polycythemia disappeared.

The effect of irradiation on the blood picture is also difficult to account for. The data reported by Lawrence in his studies on the use of radioactive phosphorus in the treatment of polycythemia suggest that irradiation has a strikingly different effect on the red cells than does either phenylhydrazine or bleeding. There is abundant evidence in the studies of investigators at the Mayo Clinic<sup>17</sup> that phenylhydrazine is a powerful hemolytic agent. Red cells are destroyed by

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16. Monge, C.: High Altitude Disease, *Arch. Int. Med.* **59**:32-40 (Jan.) 1937.

17. Giffin, H. Z., and Allen, E. V.: Experiments with Phenylhydrazine: I. Studies on Blood, *Ann. Int. Med.* **1**:655-676 (March) 1928. Allen, E. V., and Giffin, H. Z.: Experiments with Phenylhydrazine: II. Studies on Renal and Hepatic Function and Erythropoiesis, *ibid.* **1**:677-682 (March) 1928. Allen, E. V., and Barker, N. W.: Experiments with Phenylhydrazine: III. Pathological Anatomy, *ibid.* **1**:683-693 (March) 1928.



it; the nonprotein nitrogenous elements of the blood are increased temporarily after its administration; jaundice may develop, and, finally, the destroyed corpuscles are excreted, as can be shown by experiments on nitrogen excretion. Iron metabolism is so peculiarly economical, however, that iron is not lost from the body by such destruction of red cells. It may go into storage to be used over again or may be deposited in the liver, spleen or kidney. By bleeding the iron stores are actually depleted. Reimann and Breuer<sup>18</sup> have discussed this phase of the treatment of polycythemia most satisfactorily. Lawrence's report suggests that irradiation gets rid of red cells in some fashion without producing evidence either of blood destruction or of blood loss. How this occurs is not clear.

In our case, certainly, there was no apparent loss of blood following roentgen treatment. All that seemed to happen was a gratifying fall in hemoglobin concentration and blood count, with notable improvement in the patient's general sense of well-being. It is obvious, however, that our data are not sufficiently complete to exclude a slow hemolysis. That this probably occurred is suggested by the fact that eleven days after the treatment was completed, the serum iron concentration was 3.6 mg. per hundred cubic centimeters.

The true significance of our pathologic data is difficult to interpret with perfect assurance. In the literature are reported many cases of polycythaemia vera in which by one means or another the picture of the disease has been erased for varying lengths of time. The usual story is that the picture redevelops eventually. One always can claim, therefore, that our patient died of heart failure before a remission of polycythemia ended, which was either induced or spontaneous. In favor of this is the fact that histologic examination of the vertebral and the sternal marrow and of the spleen showed a degree of hematopoietic activity not ordinarily encountered in persons with chronic heart failure. On the other hand, the essential lesion, both clinical and pathologic, was that of generalized vascular disease.

Is it possible that originally polycythemia developed in our patient from abnormalities in the circulation of the bone marrow and that irradiation reduced the blood count, hemoglobin concentration and blood viscosity to normal, thereby making way for a better flow of blood, and is it possible that a permanently improved bone marrow circulation thus was stimulated, finally making our case one of healed or inactive polycythaemia vera? We incline to interpret our data in this manner and hope that this case offers promise that in certain instances polycythaemia vera may become so inactive that to all intents

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18. Reimann, F., and Breuer, A.: Die Aderlassbehandlung der Erythrämie, *Ztschr. f. klin. Med.* **128**:238-259, 1935.

and purposes the patient recovers. Other patients with known polycythemia in a state of clinical remission must be studied by the pathologist in order to throw more light on what the exact lesion in different types of polycythaemia vera may be and what the true condition really is.

On May 7, 1892, Vaquez<sup>19</sup> presented a paper before the Parisian Society of Biologists entitled, "*Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante.*" Its purpose was to call attention to the fact that there might be encountered in the clinic a peculiar group of patients without evidence of heart disease who appeared thoroughly cyanosed, who complained of a variety of

SUR UNE FORME SPÉCIALE  
DE CYANOSE S'ACCOMPAGNANT D'HYPERGLOBULIE EXCESSIVE ET PERSISTANTE,  
par M. H. VAQUEZ.

Les recherches poursuivies dans ces dernières années sur les modifications du sang et dans les maladies ont porté presque exclusivement sur les altérations globulaires, les changements d'aspect des éléments figurés, la constitution du sérum, etc.; on a noté les différentes conditions capables de provoquer la diminution du nombre des globules rouges ou l'augmentation de celui des globules blancs, mais c'est à peine si l'on a signalé la possibilité de l'hyperglobulie.

Il y a cependant des cas où le nombre des globules rouges peut être considérablement augmenté et, du fait de cette augmentation, il résulte un ensemble de symptômes qu'il est intéressant d'étudier.

Au point de vue physiologique, les auteurs ont déjà noté que le nombre des globules rouges pouvait se trouver sensiblement accru à la suite des repas (1), et par le séjour dans les hautes altitudes. M. Viault (2) a montré que dans ces conditions le nombre des globules rouges pouvait, déjà au bout de quelques jours, et suivant les personnes, atteindre 7,300,000 à 7,900,000.

Fig. 8.—The commencement of present knowledge of polycythaemia vera.

ill defined symptoms and who presented characteristically an enlarged spleen and a red cell count and hemoglobin concentration much higher than normal. The cause of this syndrome was undetermined. Major<sup>20</sup> has regarded this paper as affording a classic description of a rare disease, and it does, indeed, describe clearly for the first time what has come to be known as polycythaemia vera.

19. Vaquez, H.: *Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante*, Compt. rend. Soc. de biol. 4:384-388 (May 7) 1892.

20. Major, R. H.: *Classic Descriptions of Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 455-465.

It seems curious, as one looks backward, to realize how little attention was paid to this publication. Osler<sup>21</sup> was the first American writer to acknowledge it and then not until 1903. In this year he published a paper, "Chronic Cyanosis with Polycythaemia and Enlarged Spleen: A New Clinical Entity," and thereby aroused an interest in that group of patients first noted by Vaquez which has persisted ever since.

The literature on polycythaemia vera has grown to large proportions. It is a peculiar literature, for it reflects new currents of medical progress as they have developed, without, however, adding much to a clear understanding of what polycythaemia vera really is. Fifty years ago Vaquez expressed the hope that one day some one might be able fully to account for that form of polycythemia which he described and the cause of which he was at a loss to explain. Modern clinicians, with the many advantages which they have at hand, still are challenged to give a final answer to this question.

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21. Osler, W.: Chronic Cyanosis with Polycythæmia and Enlarged Spleen: A New Clinical Entity, *Am. J. M. Sc.* **126**:187-201 (Aug.) 1903.

# CLEARANCE OF DIODRAST, PHENOLSULFON- PHTHALEIN AND INULIN IN HYPER- TENSION AND IN NEPHRITIS

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Despite Smith's<sup>1</sup> demonstration that under proper conditions the plasma clearance of diodrast closely approximates renal plasma flow, the detection of renal ischemia in human beings is evidently not a simple matter. Its existence in patients with hypertensive disorders has been claimed by some authors<sup>2</sup> and denied by others.<sup>3</sup> This report

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1. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J. Clin. Investigation* **17**:263, 1938.

2. (a) Smith, H. W.: Studies on the Physiology of the Kidney, Porter Lecture Series, no. 9, Lawrence, University of Kansas, University Extension Division, 1939. (b) Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow and Functional Excretory Mass in Essential Hypertension, *J. Clin. Investigation* **17**:505, 1938. (c) Smith, H. W.; Goldring, W.; Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man, with Special Reference to Essential Hypertension, *Am. J. Physiol.* **123**:189, 1938. (d) Chasis, H., and Redish, J.: Unilateral Renal Function in Essential Hypertension, *J. Clin. Investigation* **20**:442, 1941. (e) Corcoran, A. C., and Page, I. H.: Renal Function in Late Toxemia of Pregnancy, *Am. J. M. Sc.* **201**:385, 1941. (f) Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Coarctation of the Aorta, *J. Clin. Investigation* **20**:107, 1941. (g) The Renal Blood Flow in Hypertension, *J. A. M. A.* **117**:92 (July 12) 1941.

3. (a) Chesley, L. C.; Connell, E. J.; Chesley, E. R.; Katz, J. D., and Glissen, C. S.: The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy, *J. Clin. Investigation* **19**:219, 1940. (b) Chesley, L. C., and Chesley, E. R.: Renal Blood Flow in Women with Hypertension and Renal Impairment, *ibid.* **19**:475, 1940. (c) Chesley, L. C.: The Question of Glomerular Damage Following Toxemia of Pregnancy, *Am. J. Obst. & Gynec.* **42**:229, 1941. (d) Welsh, C. A.; Willen, I., and Taylor, H. C., Jr.: Renal Blood Flow, Filtration Rate and Tubular Excretory Mass in Patients with Specific Toxemia of Pregnancy, *J. Clin. Investigation* **20**:438, 1941.

on a small series of subjects with normal and with diseased kidneys attempts to reconcile these divergent statements.

Since no ratios for diodrast extraction based on human material have been published, the validity of the clearance method of measuring renal blood flow clinically is not conclusively established. Indirect evidence, however, suggests that the agreement between actual blood flow and estimated blood flow is even closer in human beings than in dogs.<sup>4</sup> There being no reason to doubt that the plasma clearance of inulin is an accurate measure of the rate of glomerular filtration,<sup>5</sup> the ratio of plasma inulin clearance to plasma diodrast clearance can represent the fraction of plasma water which traverses Bowman's membrane. Hence, such other factors as membrane permeability and plasma oncotic pressure remaining constant, this ratio can vary directly with intraglomerular hydrostatic pressure and may be used to detect changes in the relative calibers of the afferent and the efferent glomerular arterioles.<sup>6</sup>

There is no doubt, for example, that the clearances of inulin and diodrast are capable of depicting the circulatory changes induced in the kidney by various pharmacologic agents. Smith's<sup>6</sup> pioneer studies in this field dramatically demonstrated the profound effects of various drugs on renal hemodynamics, and this method has been used by other investigators.<sup>7</sup> The conclusion seems logical that an agent which depresses diodrast clearance without appreciably affecting the simultaneous inulin clearance is selectively constricting the efferent glomerular arteriole, because preglomerular constriction can only diminish filtration pressure and, consequently, the inulin clearance. Under such circumstances the ratio between inulin clearance and diodrast clearance is clearly entitled to be referred to as the "filtration fraction."<sup>2a</sup>

In morbid states, however, in which the integrity of tubule function may properly be questioned, the problem is less simple. It is apparent, for example, that any factor which impairs the capacity of the renal

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4. White, H. L.; Findley, T., and Edwards, J. C.: Interpretation of Diodrast Clearances in Man, *Proc. Soc. Exper. Biol. & Med.* **43**:11, 1940.

5. Smith, W. W.; Finkelstein, N., and Smith, H. W.: Renal Excretion of the Hexitols (Sorbitol, Mannitol and Dulcitol) and Their Derivatives (Sorbitan, Iso-Mannide and Sorbide) and Endogenous Creatine-Like Chromogen in Dog and Man, *J. Biol. Chem.* **135**:231, 1940.

6. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *J. Clin. Investigation* **17**:683, 1938.

7. (a) Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, *Proc. Soc. Exper. Biol. & Med.* **46**:244, 1941. (b) Black, D. A. K.; Powell, J. F., and Smith, A. F.: Inulin and Perabrodil Clearance After Alimentary Hemorrhage in Man, *J. Physiol.* **99**:344, 1941.

tubules to secrete diodrast will also elevate the ratio of inulin clearance to diodrast clearance, even though the glomerular circulation remains unaltered. By itself, therefore, the ratio is incapable of describing the circulation pattern in diseased kidneys, several recent reports to the contrary.<sup>8</sup> We believe that in terms of renal blood flow the ratio is meaningless unless supported by a quantitative assay of the secretory power of the tubules and agree with Smith and associates<sup>9</sup> that both aspects of renal function (diodrast clearance and tubular excretion of diodrast) must be measured before one is entitled to say that the blood flow per unit of tubular tissue is or is not abnormal.

A confirmation of Smith's experience with epinephrine<sup>2a</sup> illustrates the importance of this concept (table). By using the technic described

*Effect of Epinephrine on Renal Function in a Normal Subject*

No. of Clearance Period	2/6/40					2/10/40				
	Plasma Concentration, Mg./100 Cc.		Plasma Clearance Cc./Min./1.73 Sq. Meters		Inulin Clearance/Diodrast Clearance	Plasma Concentration, Mg./100 Cc.		Plasma Inulin Clearance, Cc./Min./1.73 Sq. Meters	Tubular Secretion of Diodrast, Mg./1.73 Sq. Meters	Blood Pressure, Mm. Hg
	Dio-drast	Inulin	Dio-drast	Inulin		Dio-drast	Inulin			
1	1.35	57	511	96	0.188	66.0	54	91	31.6	105/65
2	1.27	52	510	99	0.194	63.8	49	94	31.9	108/68
3	1.21	49	416	92	0.221	62.7	47	100	31.1	108/70
1 Cc. of Solution of Epinephrine Hydrochloride (1:1,000) Administered Subcutaneously										
4	1.2	49	430	100	0.223	62.5	47	71	22.7	112/65
5	1.3	49	332	93	0.28	62.4	47	84	31.8	142/48
6	1.45	49	282	91	0.323	62.0	48	80	34.7	148/52
7	1.53	48	220	95	0.432	61.4	48	83	36.6	144/52
8	1.4	46	226	95	0.42	60.4	49	82	39.9	134/55

in the next section, consecutive fifteen minute clearance periods were obtained, the first three serving as controls. Under the established conditions epinephrine evidently reduced renal plasma flow by about 50 per cent but had no effect on the ability of the tubules to secrete iodine. In fact, the tubular secretion of diodrast actually increased, a phenomenon also noted by Smith and interpreted by him as a possible indication that new blood channels in peritubular tissue had been forced open. Now if epinephrine had reduced the tubular secretion of diodrast, it would clearly have been impossible to attribute the increased ratio between inulin clearance and diodrast clearance to ischemia alone, since diminished extractions of diodrast must also be accounted for.

8. Black, Powell and Smith.<sup>7b</sup> Footnote 2 *c*, *f* and *g*. Footnote 3 *a*, *b* and *c*.

9. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Relations of Effective Renal Blood Flow and Glomerular Filtration Rate to Tubular Excretory Mass in Normal Man, *J. Clin. Investigation* 19:739, 1940.

As an expression of the rate of plasma flow per unit of tubular excretory mass it is convenient to adopt Smith's formula, the ratio between plasma diodrast clearance and tubular excretory mass.<sup>10</sup> If this is applied to data recorded before the administration of epinephrine, a value of  $\frac{479}{31.5} = 15$  is obtained; at the height of the pressor response to epinephrine the figure drops to  $\frac{220}{36.6} = 6$ . Had the low diodrast clearance in period 7, for example, been due to diminished extraction rather than to ischemia the ratio would have remained unchanged. Our observations are inadequate to permit a statistical evaluation of normal limits, but they do show that hypertension frequently exists without demonstrable renal ischemia.

We are reporting results obtained on a relatively small series of subjects with essential hypertension and with other varieties of renal disease. We have subdivided these subjects into three clinical groups: (a) those with presumably uncomplicated essential hypertension; (b) those in whom hypertension is associated with presumptive clinical evidence of tubular damage (arteriosclerosis, retinitis, known duration of disease, diminished urea clearance, glomerulonephritis, nephrotic syndrome, congestive heart failure, abnormal urinary sediment, etc.), and (c) those with renal disease but normal blood pressure. We feel that this admittedly arbitrary arrangement has facilitated interpretation of the data.

#### METHODS

On the morning of the test, food, medication and tobacco were withheld from all subjects. Adequate hydration and diuresis were assured by the oral administration of at least 1 liter of water about an hour before the first collection of urine and by the subsequent ingestion of 200 cc. every half hour. In every case the body temperature was within 1 degree of 37 C. (98.6 F.). Urine was collected through an indwelling catheter and the bladder washed three to five times with 20 cc. portions of physiologic solution of sodium chloride. In order to diminish emotional factors the urethra was always anesthetized, and in many cases venipuncture was also done with the area under local anesthesia. Blood pressure was recorded at frequent intervals.

Before each infusion a sample of blood was obtained, part of which served as an inulin blank: to the plasma of another portion a known amount of diodrast was added, and the percentage of iodine recoverable in trichloroacetic acid filtrate was determined. All samples of blood were treated with heparin, and the plasma was separated as soon as possible. Determinations of diodrast iodine were done either by the original<sup>11</sup> or by the modified<sup>12</sup> method of White and Rolf. Inulin

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10. Smith, H. W.; Chasis, H.; Goldring, W., and Ranges, H. A.: Glomerular Dynamics in the Normal Human Kidney, *J. Clin. Investigation* **19**:751, 1940.

11. White, H. L., and Rolf, D.: A Rapid Micro-Method for Determining Diodrast and Inorganic Iodide Iodine in Blood and Urine, *Proc. Soc. Exper. Biol. & Med.* **43**:1, 1940.

12. White, H. L., and Rolf, D.: Modified Method for Determination of Certain Organic Iodine Compounds, Inorganic Iodide in Plasma and Urine, *Proc. Soc. Exper. Biol. & Med.* **45**:433, 1940.

was determined by a slight modification of the method of Corcoran and Page.<sup>13</sup> Phenolsulfonphthalein also was estimated by the method of Corcoran and Page.<sup>14</sup> Urea clearance was determined by the hypobromite method without permutit (a hydrated sodium aluminum silicate).<sup>15</sup>

The actual procedure was essentially that devised by Smith and associates.<sup>9</sup> Infusions were delivered from a gravity bottle to which was attached a small calibrated side arm tube; this permitted a quick and accurate check on the rate of flow, changes in which were governed by a tunnel clamp on the outlet tubing. For determination of renal blood flow the following plasma concentrations were desired per hundred cubic centimeters: diodrast iodine, 1 to 5 mg.; inulin, 8 to 15 mg. and phenolsulfonphthalein, 0.5 to 1.0 mg. In the average adult these were usually achieved by (a) a priming solution made by adding 1.5 cc. of diodrast<sup>16</sup> and 0.5 cc. of 10 per cent phenolsulfonphthalein to the contents of a 50 cc. ampule of 10 per cent inulin,<sup>17</sup> the intravenous injection of which occupied five minutes, or (b) a sustaining solution consisting of 1 per cent diodrast, 0.5 per cent inulin and 0.8 per cent phenolsulfonphthalein in physiologic solution of sodium chloride delivered at the rate of 4 cc. per minute. In case of manifest renal insufficiency the infusion rate was reduced to 1 or 2 cc. per minute. To insure equilibration the infusion was continued for twenty minutes before the first collection of urine was begun. At that time the first sample of blood was drawn, the urine in the bladder was discarded and consecutive ten to twenty minute clearance periods were obtained in the usual way. Midperiod plasma concentrations of diodrast iodine, phenolsulfonphthalein and inulin were found by interpolation from at least three actual analyses, all done in duplicate. The flow of urine was such that all urea clearances were maximum.

The conditions for determining the tubular secretion of diodrast were established by injection through a syringe of 0.3 cc. of diodrast per kilogram of body weight, the injection requiring from three to five minutes. The second sustaining fluid consisted of 10 per cent diodrast and 0.5 per cent inulin in physiologic solution of sodium chloride, the rate of flow being continued as before. This usually resulted in a concentration of 25 to 30 mg. of diodrast iodine per hundred cubic centimeters of plasma, a level well above that at which tubular saturation occurs.<sup>18</sup>

Hematocrit readings were obtained on every sample of blood to permit calculation of renal whole blood flow by the ratio of plasma diodrast clearance to the plasma volume in percentage. We are aware that Smith and Smith<sup>19</sup> reported that plasma protein binds a small amount of diodrast and thus renders it unavailable for glomer-

13. Findley, T., and White, H. L.: Measurement of Diodrast and Inulin Clearances in Man After Subcutaneous Administration, *Proc. Soc. Exper. Biol. & Med.* **45**:623, 1940.

14. Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance, *Am. J. Physiol.* **126**:354, 1939.

15. Van Slyke, D. D.; Page, I. H.; Hiller, A., and Kirk, E.: Comparison of Urea Clearances Calculated from the Excretion of Urea, of Plus Ammonia, and of Nitrogen Determinable by Hypobromite, *J. Clin. Investigation* **14**:901, 1935.

16. The diodrast was supplied by the Winthrop Chemical Co., Inc., New York.

17. The inulin was supplied by Standard Products Co., Woodworth, Wis.

18. Smith, Goldring and Chasis.<sup>1</sup> White, Findley and Edwards.<sup>4</sup>

19. Smith, W. W., and Smith, H. W.: Protein Binding of Phenol Red, Diodrast and Other Substances in Plasma, *J. Biol. Chem.* **124**:107, 1938.



ular filtration, whereas Elsom, Bott and Shiels<sup>20</sup> considered that all plasma diodrast was free; in calculating the glomerular excretion of diodrast we have used the Smith nomogram,<sup>19</sup> but we realize that even at the high plasma concentrations necessary for determination of the tubular excretory mass the difference is almost negligible. When the concentration of albumin in the plasma was found by actual analysis to be less than 4 Gm. per hundred cubic centimeters, calculations were based on the observed value; otherwise a uniform value of 4 Gm. was arbitrarily used.

#### RESULTS ON NORMAL SUBJECTS

We have examined 17 men, all healthy medical students or laboratory assistants less than 40 years of age, with maximal urea clearances greater than 50 cc. per minute per 1.73 square meters. Data were obtained on every subject for at least three consecutive periods. All values are referred to a surface area of 1.73 square meters.

*Plasma Diodrast Clearance.*—The average diodrast clearance for one hundred periods in 17 subjects is 544 cc. per minute, with extremes of 402 and 785 cc. This is a little higher than a previous estimate by some of us<sup>4</sup> of 497 cc. per minute in 11 subjects. It agrees well with Chesley's latest report<sup>3c</sup> of 567 cc. in normal women and with the value 537 cc. obtained by Black, Powell and Smith<sup>7b</sup> presumably on mixed subjects. It is still appreciably lower for some reason than the latest estimate by Smith and associates<sup>9</sup> of 688 cc. in normal men.

*Whole Blood Flow.*—From the same material our average value for whole blood flow is 1,010 cc. per minute, with extremes of 821 and 1,380 cc., as compared with Smith's value of 1,189 cc. per minute.

*Plasma Inulin Clearance.*—For ninety-nine periods in 12 subjects the average value for inulin clearance is 117 cc. per minute, with extremes of 71 and 173 cc.

*Ratio of Plasma Inulin Clearance to Plasma Diodrast Clearance.*—As determined through forty-one periods in 11 subjects the average value for this ratio is 0.205, with extremes of 0.138 and 0.261.

*Tubular Secretion of Diodrast.*—For forty-seven periods in 9 subjects the average rate of tubular secretion of diodrast iodine is 40.1 mg. per minute, with extremes of 35 and 47.9 mg. This is also appreciably lower than the value of 53.3 mg. per minute recently reported by Smith and associates.<sup>9</sup> In every instance diodrast was presented to the tubules at a rate (renal plasma flow  $\times$  plasma diodrast [milligrams per cubic centimeter] — glomerular excretion of diodrast [milligrams per minute]) at least 30 per cent in excess of the rate of secretion of iodine by the tubules.

20. Elsom, K. A.; Bott, P. A., and Shiels, E. H.: On the Excretion of Skiodan, Diodrast and Hippuran by the Dog, *Am. J. Physiol.* **115**:548, 1936.

*Ratio of Plasma Diodrast Clearance to Tubular Secretion of Diodrast.*—With a numerator obtained on 17 subjects and a denominator obtained on 9 subjects the average is 13.56, as compared with Smith's reported value of 13.6.

*Ratio of Plasma Inulin Clearance to Tubular Secretion of Diodrast.*—On the basis of gross averages from the aforementioned data the figure is 2.91 (Smith, 2.57).

*Plasma Phenolsulfonphthalein Clearance.*—Our experience with this substance is too limited to justify much comment, since we have used it on only 14 subjects, 12 of whom were abnormal. Its use was abandoned because it seemed to us to offer little additional information. We have not corrected our diodrast clearances for possible depression due to interference of phenolsulfonphthalein because in every instance the concentration of this substance in the plasma was less than 1 mg. per hundred cubic centimeters.

In 2 normal men the average plasma clearance of phenolsulfonphthalein in thirteen periods was 295 cc. per minute, with extremes of 265 and 354 cc. This is again lower than the mean value of 394 cc. obtained by Smith and associates on a much larger series.<sup>1</sup> The average value for the ratio of plasma phenolsulfonphthalein clearance to plasma diodrast clearance is 0.626.

*Tubular Secretion of Phenolsulfonphthalein.*—We have determined this on only 1 normal subject for obvious reasons. Tubular saturation occurred at a plasma concentration of about 15 mg. per hundred cubic centimeters, and the maximal rate of tubular secretion during four periods averaged 19.4 mg. per minute. Smith and associates<sup>1</sup> reported a rate of 35.8 mg. per minute in 1 case.

Since the ratio between plasma phenolsulfonphthalein clearance and plasma diodrast clearance in our small series of hypertensive subjects appeared to offer little information of value, no further reference to phenolsulfonphthalein will be made.

#### RESULTS ON ABNORMAL SUBJECTS

Our data on 28 patients with miscellaneous renal lesions are presented in chart 1. In order to facilitate comparison we use essentially the same graphic method employed by Smith,<sup>2a</sup> wherein points are arranged semilogarithmically along arbitrarily placed slanting lines. It should be particularly noticed that the values for tubular secretion of diodrast are so arranged that they fall exactly on the line; the points which represent simultaneous diodrast and inulin clearances and ratios of inulin clearance to diodrast clearance are easily found by projecting a vertical line through the point for tubular secretion of diodrast.

The open circles represent 12 subjects with presumably uncomplicated essential hypertension; i. e., they are all less than 50 years of age, they have normal urea clearances and urinary sediments and parenchymal damage is minimal so far as one is able to predict from the appearance of the eyegrounds, the absence of cardiac involvement, etc. These are the subjects in whom it is reasonable to suppose that any depression in diodrast clearance is apt to represent diminished blood flow rather than tubular damage.

The solid circles represent 12 subjects in whom hypertension is accompanied by evidence of organic renal disease. Three had chronic glomerulonephritis; 4 had cardiac involvement with mild congestive

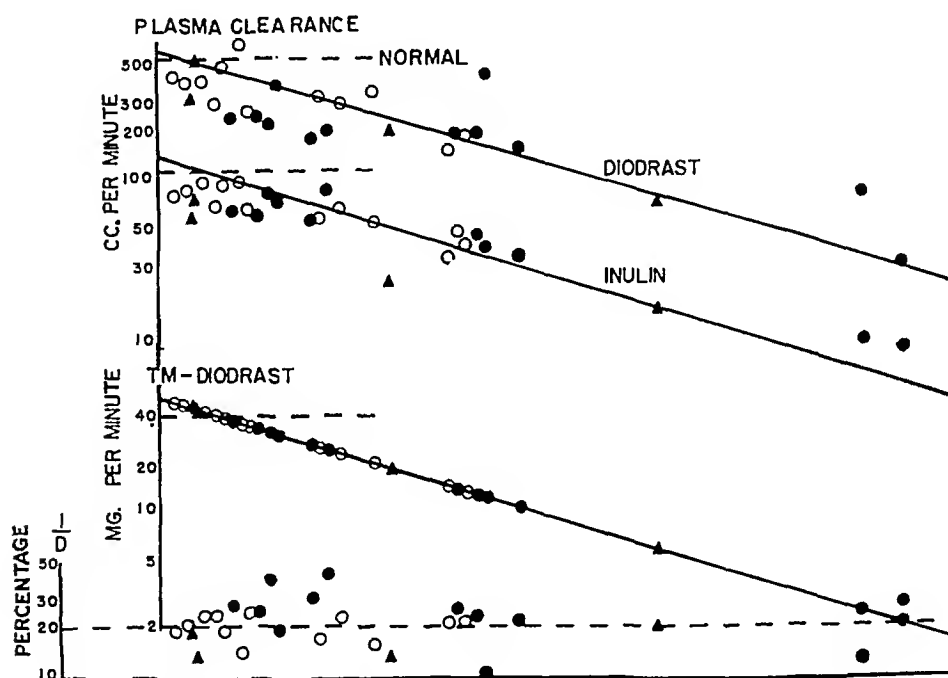


Chart 1.—Relation of tubular secretion of diodrast (*TM-Diodrast*) to diodrast clearance, inulin clearance and the ratio ( $\frac{I}{D}$ ) of these two clearances to each other (see text). The horizontal lines indicate our normal averages; the open circles, subjects with uncomplicated hypertension; the solid circles, patients with advanced hypertension, and the triangles, patients with renal disease and normal blood pressure. If all values were displaced proportionally to tubular secretion of diodrast, they would fall on their respective slanting lines.

heart failure; 3 were more than 60 years of age and had marked arteriosclerosis with subnormal urea clearances, and 2 had uremia and the retinal picture of malignant hypertension.

The triangles account for 4 patients with renal disease but normal blood pressure. One had marked peripheral arteriosclerosis and slight proteinuria; 1 had syphilitic nephrosis, from which he recovered; another had chronic glomerulonephritis of many years' duration and a biliary

fistula, and the fourth had severe congestive heart failure with albuminuria, azotemia and jaundice, from which he also recovered.

Because of insufficient data we are unable to define statistically the limits of normal, but it is apparent that at least 7 of the 12 subjects with uncomplicated hypertension have values for tubular secretion of diodrast so close to our normal average that we are forced to assume that tubular function, as measured by the capacity for diodrast secretion, is intact. We must emphasize the fact that all of these patients were under continuous observation in the hospital and had sustained blood pressure readings in excess of 150 systolic and 100 diastolic.

None of these 12 subjects shows an elevated ratio of inulin clearance to diodrast clearance. Half of the plasma diodrast clearances fall somewhat below the predicted level but not in disproportion to the fall in corresponding inulin clearance. This is in contrast to the results obtained on 12 subjects with advanced hypertension, about half of whom exhibited ratios higher than our normal average. It is in this group that interpretation of data becomes difficult. A few deductions seem justifiable. Proportionate reductions in the clearance of diodrast and inulin and in tubular secretion of diodrast do not produce changes in either the ratio of inulin clearance to diodrast clearance or the ratio of diodrast clearance to tubular secretion of diodrast and indicate simply the presence of small kidneys; in this category we place the remaining 5 subjects with uncomplicated hypertension. Spasm of the efferent glomerular arterioles would, as in the experiments with epinephrine, so reduce diodrast clearance as to increase the ratio of inulin clearance to diodrast clearance and diminish the ratio of diodrast clearance to tubular secretion of diodrast; 5 subjects with advanced hypertension appear to fall in this class, but there is no assurance that impaired renal extraction is not a factor. Indeed, there is every reason to suppose that the kidneys of patients with the stated clinical characteristics would be unable to handle diodrast loads normally. We see no way to separate these two factors clearly, but the high ratios of inulin clearance to diodrast clearance and normal values for the ratio of diodrast clearance to tubular secretion of diodrast in the 3 other subjects in this group seem best explained by assuming that impaired tubular extraction is more important than arteriolar spasm as a cause of diminished excretion of diodrast.

Among the 4 normotensive patients there are 2 with normal and 2 with subnormal ratios of inulin clearance to diodrast clearance. Of the 2 subjects with normal values the one in whom the tubular secretion of diodrast iodine is 6 mg. per minute had severe congestive heart failure and the other (tubular secretion of diodrast iodine, 42 mg. per minute) was well except for senile arteriosclerosis and slight proteinuria: in neither patient is there reason to postulate selective damage to either

glomeruli or tubules. Of the 2 subjects with low ratios between inulin clearance and diodrast clearance, 1 had nephrosis and intense proteinuria and the other had chronic glomerulonephritis; in both altered membrane permeability may have retarded the rate of filtration.

In chart 2 the ratios between inulin clearance and diodrast clearance are plotted against the ratios of diodrast clearance to tubular secretion of diodrast in an effort to detect any relation between the so-called "filtration fraction" and the degree of renal ischemia. In general, there appears to be an inverse relation, but again only half of the 24 patients

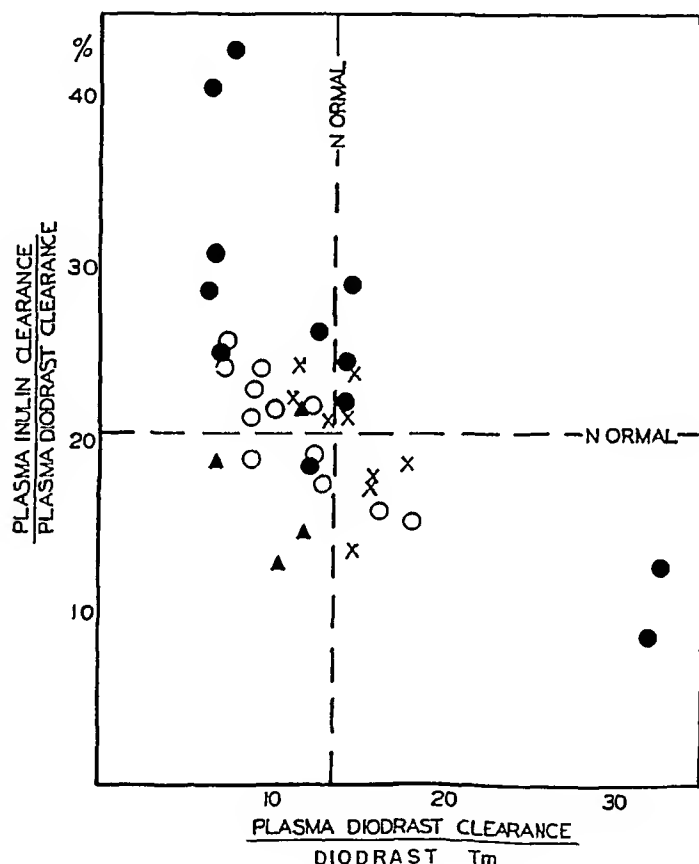


Chart 2.—Relation between the ratio of inulin clearance to diodrast clearance and renal ischemia (see text). The broken lines indicate our normal averages, and X signifies the normal subjects. For the significance of the other symbols see chart 1. *Diodrast Tm* signifies tubular secretion of diodrast.

with hypertension have a ratio of diodrast clearance to tubular secretion of diodrast of less than 10, our lowest normal value. Of the 6 patients who exhibit both ischemia and a high ratio of inulin clearance to diodrast clearance, only 1 falls in the uncomplicated group. Seven of the 8 in whom this ratio exceeds 0.25 have advanced renal disease. The 4 whose ratios are less than 0.15 all have primary glomerular

disease, though only 2 of them also have hypertension, and these 2 are the only ones of the entire series whose conditions plainly fall in the zone of relative hyperemia.

## COMMENT

This failure to find consistently abnormal renal circulation patterns in subjects with essential hypertension is at variance with the reports of the originators of the method; we are reluctant to draw dogmatic conclusions, particularly since our material is so limited. The mere fact, however, that even this small experience has disclosed a high percentage of patients with essential hypertension with normal clearance and normal tubular secretion of diodrast appears to lend support to the conclusion reached by others from studies on nephritis and the toxemias of pregnancy that demonstrable renal ischemia is not a constant factor in the genesis of high blood pressure and to the recent perfusion studies of Cox and Dock.<sup>21</sup> This is not to say, of course, that no disturbance in renal blood flow exists in these conditions; the experimental studies of Kohlstaedt and Page<sup>22</sup> have shown that hypertension may depend primarily on diminution of pulse pressure within the kidney rather than on an absolute reduction in total blood flow. If one considers also the well known difficulties encountered in demonstrating renal ischemia even in animals the renal arteries of which are mechanically occluded,<sup>23</sup> it may be that too much is being asked of the clearance method.

We do not think we have been too rigid in selecting our subjects with uncomplicated hypertension, for in every instance the diagnosis was, first made by a member of the regular house staff of the hospital. We also wish to point out that the selection of the subjects with advanced or with complicated hypertension was made clinically and was not arbitrarily based on the magnitude of the ratio of inulin clearance to diodrast clearance. Yet the correlation seems clear, and we are inclined to attribute disproportionate reduction of diodrast clearance to impaired tubular extraction of diodrast rather than to increased intraglomerular pressure dependent on efferent arterial spasm. This, however, is a matter of probability rather than of demonstrated fact.

As for glomerulonephritis, we have complete data on only 4 subjects, in all of whom the condition is chronic. There is marked individual

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21. Cox, A. J., Jr., and Dock, W.: The Capacity of the Renal Vascular Bed in Hypertension, *J. Exper. Med.* **74**:167, 1941.

22. Kohlstaedt, K. G., and Page, L. H.: Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, *Proc. Soc. Exper. Biol. & Med.* **43**:136, 1940.

23. Page, I. H.: Newer Aspects of Experimental Hypertension in Blood, Heart and Circulation: Symposium, Publication 13, American Association for the Advancement of Science, 1940, p. 239.

variation, of course, but all showed low ratios between inulin clearance and diodrast clearance, none had subnormal ratios between diodrast clearance and tubular secretion of diodrast and 2 of those with more advanced glomerulonephritis had conditions definitely in the hyperemia zone. The interpretation of these data is clouded by the theoretic possibilities of aglomerular tubules, "impotent" tubules and arteriovenous shunts, and we prefer simply to record the data.

### CONCLUSIONS

Values for renal blood flow, glomerular filtration rate and tubular secretion of diodrast are reported on a series of normal subjects and patients with essential hypertension, glomerulonephritis and other types of renal disease.

Plasma clearances of diodrast and inulin, even when interpreted in the light of tubular secretion of diodrast, indicate absence of renal ischemia in a high proportion of subjects with uncomplicated essential hypertension.

Under controlled conditions the ratio between inulin clearance and diodrast clearance can represent the "filtration fraction," but high ratios in subjects with hypertension probably result from diminished diodrast extraction rather than from increased filtration pressure.

NOTE.—Since this manuscript was completed, more reports by Smith and his co-workers have appeared.<sup>24</sup> Our findings appear to be in general agreement, although these authors would evidently exclude from consideration any subject who has a high ratio of inulin clearance to diodrast clearance but a normal ratio of diodrast clearance to tubular secretion of diodrast on the grounds that "impotent nephrons will produce a vicarious hyperemia in such functional tissue as may be perfused by the vestigial vascular channels related to the now defunct tissue."<sup>24b</sup> It may be that the conversion of isolated tubules into "passive conduits" is common in Bright's disease, but we have preferred to regard diminished diodrast extraction as a consequence of diffuse parenchymal degeneration. However that may be, its existence makes detection of coexisting renal ischemia by the clearance method difficult or impossible, since blood from the renal veins is unobtainable in human beings. These investigators<sup>24b</sup> have, moreover, reported on 3 hypertensive subjects with normal clearance and normal values for the tubular secretion of diodrast. If these are added to our subjects with uncompli-

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24. (a) Smith, H. W.: Note on the Interpretation of Clearance Methods in the Diseased Kidney, *J. Clin. Investigation* 20:631, 1941. (b) Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects with Essential Hypertension, *ibid.* 20:637, 1941. (c) Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, *ibid.* 20:655, 1941.

cated hypertension in whom both the ratio of inulin clearance to diodrast clearance and the ratio of diodrast clearance to tubular secretion of diodrast are normal, it appears difficult to believe that renal ischemia is a constant feature in this disorder. Although our absolute values for diodrast clearance and tubular secretion of diodrast are, for some unknown reason, consistently lower than those reported by Smith and associates, it should again be noted that our normal ratios between diodrast clearance and tubular secretion of diodrast are practically identical with theirs.

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# CRITICAL STATISTICAL ANALYSIS OF DATA ON RENAL FUNCTION IN GROUPED SUBJECTS WITH ESSENTIAL HYPERTENSION

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We have made a statistical study of the renal function of patients with essential hypertension. The only large series of data available to us from tests of renal function are chiefly results of the Volhard, the phenolsulfonphthalein excretion and the urea clearance test. It has been shown by a number of investigators<sup>1</sup> that these tests do not demonstrate remarkable reductions in renal function in persons with essential hypertension. On studying the reports on which this conclusion was based, it was evident that the opinion was obtained as a result of comparing single examples of renal function in persons with essential hypertension with single examples of renal function in a normal person in an attempt to demonstrate differential diagnostic possi-

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From the Cardiovascular-Renal Research Department, Santa Barbara Cottage Hospital.

1. (a) Leiter, L.: Renal Function in Studies from the Lasker Foundation for Medical Research, Chicago, 1930-1937, vol. 1, no. 10. (b) Pratt, J. H.: Dilution and Concentration Tests of Renal Function, Boston M. & S. J. **195**:203-207 (July 29) 1926. (c) Ellis, L. B., and Weiss, S.: Normal Variations in Renal Function with a Discussion of Their Physiological Significance, Am. J. M. Sc. **186**:233-242, 1933; (d) Renal Function in Persons with One Kidney, *ibid.* **186**:242-248, 1933; (e) Renal Function in Arterial Hypertension, J. A. M. A. **100**:875-878 (March 25) 1933. (f) Chapman, E. M., and Halstead, J. A.: Fractional Phenolsulphonphthalein Test in Bright's Disease, Am. J. M. Sc. **186**:223-232, 1933. (g) Van Slyke, D. D.; Stillman, E.; Modler, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; Mackon, E. M.; Hannon, R. R., and Moore, N. S.: Observation on the Course of Different Types of Bright's Disease and on the Resultant Change in Renal Anatomy, Medicine **9**:257-386, 1930. (h) Kisch, F.: Essential Hypertension and the Kidneys, Wien. Arch. f. inn. Med. **9**:1, 1925; abstracted, J. A. M. A. **84**:239 (Jan. 17) 1925. (i) Major, R. H.: Renal Function in Arterial Hypertension, Am. J. M. Sc. **176**:637-644, 1928. (j) Musser, J. H., and Phillips, A. W.: A Comparison of Blood Pressure, Blood Urea Nitrogen, Phenolsulphonphthalein and Urine Tests in the Aged, J. Lab. & Clin. Med. **15**:632-637, 1930. (k) Buck, R. W., and Proger, S. H.: Dilution and Concentration Test of Renal Function, New England J. Med. **203**:1283-1288 (Dec. 25) 1930. (l) Freyberg, R. H.: The Choice and Interpretation of Tests of Renal Efficiency, J. A. M. A. **105**:1575-1580 (Nov. 16) 1935.

bilities of the tests. We have tried other methods of analysis in order to exhaust the possibilities of these tests.

The purpose of this paper is to demonstrate that in spite of apparently small differences from normal there exists a significant reduction in the ability of the kidneys of patients with essential hypertension to concentrate urine and to excrete phenolsulfonphthalein. This reduction can be demonstrated only when the study includes data on hypertensive patients and on normal persons considered collectively for the respective groups instead of singly in individual comparisons. In addition, it will be shown that the age of the patient and the duration of the disease have no effect on the renal function either of normal or of hypertensive persons. It will be shown that increase in the severity of the disease, as indicated by a rise in diastolic pressure, is accompanied by reduction in renal function. It will also be demonstrated that the use of alkaline diets apparently causes delay in excretion of fluids.

#### METHOD

As reported before the Sixth Pacific Science Congress,<sup>2</sup> we have performed tests of renal function on a group of 100 patients with essential hypertension and have compared the results with those obtained from tests on a group of normal subjects. In this study case histories of hospitalized patients were selected, each of whom had been subjected to at least six of eight different tests of renal function. At the time of the tests precautions were taken to eliminate extrarenal factors that might affect the outcome. Previous intake of nutrients was controlled,<sup>1b</sup> and dehydration through exercise and nervousness was prevented. Patients with anasarca were excluded. Extreme care was exercised in the collection of samples of urine, and drugs, such as sodium bicarbonate, were not given in a test period. Phenolsulfonphthalein excretion, urea clearance and the ability of the kidneys to concentrate the urine were measured in the following manner:

1. Phenolsulfonphthalein,<sup>3</sup> accurately measured in a tuberculin syringe, was given intravenously after emptying of the bladder and ingestion of 600 cc. of water. The result was reported in terms of the amount excreted at the end of two hours.

2. The recommended technic for measuring urea clearance was strictly adhered to.<sup>4</sup> Four hundred cubic centimeters of water was ingested at the beginning of the test in the hope of securing a maximum secretion, but frequently the rate

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2. Dalton, J. W., and Nuzum, F. R.: Some Evidence of Impaired Function of the Kidney in Individuals with Essential Hypertension, *Proc. Sixth Pacific Sc. Cong.*, to be published.

3. Rountree, L. G., and Geraghty, J. T.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, *J. Pharmacol. & Exper. Therap.* **1**:579-661, 1910.

4. Møller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies in Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6**:427-465, 1928.

of formation of urine fell below 2 cc. per minute. The values obtained for the first and the second hour were averaged. The result was expressed in terms of the percentage of normal.

3. The concentration test of Volhard<sup>5</sup> was begun at 7 a. m. after the bladder had been emptied. The subject consumed quickly 1,000 cc. of water flavored with orange juice. Thereafter, a dry diet was given. Specimens of urine were collected at two hour intervals until 7 p. m. A single specimen was collected between 7 p. m. and 7 a. m. The volume of urine was measured within 5 cc. by standardized hydrometers, with correction for changes in temperature when indicated.

The six hour output, the total day output and the total night output of urine, originally divisions of the Volhard test, are listed under separate headings for the sake of clarity and ease of study. In consideration of the effect of diet other tests include the twenty-four hour output of urine and the  $\rho H$  of the urine.

After applying formulas applicable to groups of random samples, the statistical analysis was made by the computation of the means of the standard deviations through the use of the respective formulas of Fisher<sup>6</sup> and Burn.<sup>7</sup> Because of the large volume of calculation and the limitation of space, the positive results are summarized in suitable tables. All negative results have been previously reported in detail.<sup>2</sup>

#### OBSERVATIONS

Before comparing the results of renal function tests on a group of hypertensive patients with the results of the same tests on normal subjects, four variable conditions should be considered. The first of these variable conditions is the effect of the age of the subject on the function of the kidney. This variable is discharged in the following arrangement.<sup>8</sup> The samples are grouped according to decades in order to determine the significance of age in the variations of the readings.

Age, Yr.	Number of Subjects	
	Hypertensive	Normal
20 - 30	6	7
31 - 40	7	9
41 - 50	19	6
51 - 60	24	10
61 - 70	35	6
71 - 80	9	6
	—	—
	100	44

A comparison is made, first, between the results of the renal function tests on patients with hypertension and the results of the same tests

5. Volhard, F., and Suter, F.: *Nieren und ableitende Harnwege*, Berlin, Julius Springer, 1931, p. 165.

6. Fisher, R. A.: *Statistical Methods for Research Workers*, London, Oliver & Boyd, 1930, p. 46.

7. Burn, J. H.: *Errors in Biological Assay*, *Physiol. Rev.* **10**:165, 1930.

8. Fisher,<sup>6</sup> p. 107.

on normal subjects of the same decades. In continuing the test of the effect of age on renal function, another method is used. Comparison of the means of the results of tests on patients with hypertension of two consecutive decades is made, as well as a like comparison for the normal subjects of the same two periods. This is accomplished by a simple rearrangement of the data so that the 6 hypertensive patients of the decade 20-30 are compared with the hypertensive subjects of the decade 31-40, and so on. In like manner, the 7 normal subjects of the decade 20-30 are compared with the 9 normal subjects of the decade 31-40. In these studies of the effect of age on the function of the kidney the chances of an insignificant difference in both series occurred as often as one time in sixty, or even more frequently.<sup>2</sup> It is felt that such an occurrence is too frequent and that apparent differences due to age are fortuitous.

The second of the four important variables affecting the study of renal function in essential hypertension is the relation of the duration of the process to the degree of impairment of renal function. The data on the patients with hypertension are arranged by test into six groups, one for each of the following tests: total day output of urine, total night output of urine, six hour output of urine, specific gravity difference, phenolsulfonphthalein excretion and urea clearance. Each of the six groups is divided according to the known duration of the disease into the following eight divisions: durations of one, two, three, four, five, six to nine, ten to fourteen and fifteen to eighteen years, respectively. The results of the determinations of all other divisions are compared separately with those of the first division, one year's duration. These collations have been published.<sup>2</sup> The one computation in this study which proved existence of actual differences was the phenolsulfonphthalein excretion for the division six to nine years' duration when compared with that for the division one year's duration. It must be remembered that there are forty-one other computations in this group of determinations testing this variable. Thus, one positive result in forty-two calculations is not outstanding, and one is forced to conclude that the duration of essential hypertension has no effect on the degree of impairment of function.

The third important variable to study is the coexistence of varying degrees of hypertension and changes in renal function, as shown by the same tests. The data on all hypertensive patients are arranged in six groups, one for each test used. Each of these groups has three divisions. Data on patients whose blood pressures were recorded as under 200 systolic and 99 diastolic are used as a basis of comparison. To this standard, in the first division, are compared data for the group having the same systolic pressures but having diastolic pressures ranging from 100 to 140. In the second and the third division to the data for the standard group are compared results for groups in which the systolic pressures are over 200 and the diastolic pressures are, respectively,

100 to 140 and 140 to 176. In table 1 is the summation of the results of these comparisons of the effects of extremes of hypertension on renal function.

In the third division in the phenolsulfonphthalein test the value for *P* (probability of insignificant difference) is less than 0.01. In the specific gravity test for the same division this value is just greater than

TABLE 1.—*Effect of Degree of Hypertension on Renal Function* \*

Test		Degree of Hypertension		
		Systolic 150 - 200, Diastolic 100 - 140	Systolic 200 or More, Diastolic 100 - 139	Systolic 200 or More, Diastolic 140 - 176
Total day output of urine.....	x	1,034.1 cc.	1,034.1 cc.	1,034.1 cc.
	y	962.1 cc.	932.5 cc.	919.5 cc.
	x-y	72.0 cc.	101.6 cc.	114.6 cc.
	n	63	45	37
	P	0.4	0.4	0.4
Total night ouput of urine.....	x	315.7 cc.	315.7 cc.	315.7 cc.
	y	367.2 cc.	355.8 cc.	522.9 cc.
	x-y	51.5 cc.	40.1 cc.	207.2 cc.
	n	63	45	36
	P	0.4	0.4	0.02
Six hour output of urine.....	x	794.4 cc.	794.4 cc.	794.4 cc.
	y	675.1 cc.	675.1 cc.	517.6 cc.
	x-y	119.3 cc.	119.3 cc.	276.8 cc.
	n	61	45	37
	P	0.1	0.1	0.02
Specific gravity difference.....	x	1.0171 Gm./cc.	1.0171 Gm./cc.	1.0171 Gm./cc.
	y	1.0179 Gm./cc.	1.0162 Gm./cc.	1.0116 Gm./cc.
	x-y	-0.0008 Gm./cc.	0.0009 Gm./cc.	0.0055 Gm./cc.
	n	61	45	37
	P	0.7	0.5	0.01 †
Phenolsulfonphthalein excretion...	x	59.0%	59.0%	59.0%
	y	59.2%	54.2%	37.5%
	x-y	-0.2%	4.9%	21.5%
	n	62	45	37
	P	0.9	0.2	0.01 †
Urea clearance, per cent of normal	x	65.8	65.8	65.8
	y	63.2	60.0	64.4
	x-y	-2.4	5.8	1.4
	n	63	45	37
	P	0.7	0.7	0.9

\* The following symbols have been employed: *P*, the probability of insignificant difference; *n*, the number of samples (both of *x* and *y*); *x*, the means of the results of tests on hypertensive patients with systolic pressures of 150 to 200 and diastolic pressures from normal to 99, and *y*, the means of the results of tests on hypertensive patients with systolic and diastolic pressures as indicated in the three columns under the heading Degree of Hypertension.

† Any difference in means that is significant is indicated by a value for *P* of 0.01 or less.

0.01. Therefore, the chances of an insignificant difference occurring are less than one in one hundred and between one in fifty and one in one hundred, respectively. The chances of an insignificant difference are nearly one in fifty in the total night output test and the six hour output test in the same division, as indicated by values for *P* of 0.02. Four differences in the foregoing study are important. As the number of samples is large, it is only necessary to test these four computations

by a more accurate method.<sup>9</sup> The results of the new calculations are shown in table 2.

The values obtained from the two tests are comparable. The quantity for *P* is determined, which again indicates the chances for insignificant difference. There is complete substantiation of the results of the phenol-sulfonphthalein excretion test in this new computation. The six hour output test, likewise, shows a real difference between the two means of the two extremes of hypertension. The total night output test and the specific gravity test allow an insignificant difference between the two means of one to five and one to twenty, respectively. In this more accurate study there are two instances out of eighteen computations in which unquestionable differences between means occur.

TABLE 2.—*Effect of Degree of Hypertension on Renal Function \**

Test	Degree of Hypertension		
		Systolic 150 to 200, Diastolic Normal to 99	Systolic 200 or Over, Diastolic 140 to 178
Total night output of urine	Mean.....	315.7 cc.	522.9 cc.
	Standard deviation of the mean	27.4	149.5
	Difference.....		207.2 cc.
	P.....		0.18
Six hour output of urine	Mean.....	794.4 cc.	517.6 cc.
	Standard deviation of the mean	74	63.1
	Difference.....		276.8 cc.
	P.....		0.01 *
Specific gravity difference	Mean.....	1.0171 Gm./cc.	1.0116 Gm./cc.
	Standard deviation of the mean	0.0009	0.0026
	Difference.....		0.0055 Gm./cc.
	P.....		0.05
Phenolsulf- onphthalein excretion	Mean.....	59.0%	37.5%
	Standard deviation of the mean	2.90	6.0
	Difference.....		21.5%
	P.....		0.01 *

\* Any difference in means is significant if indicated by a value for *P* of 0.01 or less.

The fourth variable which should be considered is the effect of the alkalinity of the diet on the function of the kidney in hypertension. All of the patients with hypertension mentioned so far are from a group studied since 1932. These patients were given a general diet, the ash of which was neutral. They were not given alkaline medication. Prior to 1932, as a result of studies on 1 of us,<sup>10</sup> all patients with essential hypertension were placed on basic or semibasic diets. The renal function of these patients on alkaline diets was studied through the use of the Volhard concentration and the phenolsulfonphthalein excretion

9. Fisher,<sup>6</sup> pp. 101-102. Burn,<sup>7</sup> p. 168.

10. Nuzum, F. R.; Sansum, W. D., and Osborne, M.: The Experimental Production of Hypertension, *Arch. Int. Med.* 35:497-499 (April) 1925.

test only. The sole test of the effect of the diet as an alkalinizing agent was the determination of the  $p_H$  of the urine. If more than one reading of the  $p_H$  was taken, an average was made. All patients were on the alkaline diet for one month before observations were started. The results of the tests from 36 records, from 1928 to 1932, are analyzed statistically and compared with the records of the same tests on a group of 71 patients, selected at random from the 100 patients with hypertension who were on the general diet. Because of the limited series of patients on the alkaline diet no subjects in the early adult years are included. This should make little difference, for it has been shown that age does not affect the function of the kidney as illustrated by the six tests of renal function considered. The data are derived from the results of the tests on patients in the following decades:

Decade	No. of Subjects	
	General Diet	Alkaline Diet
41 - 50	10	5
51 - 60	24	12
61 - 70	28	14
71 - 80	9	5
	—	—
	71	36

The appropriate formula <sup>11</sup> is applied to the means and the standard deviation of the means of the two larger groups in order to determine the standard error. The results are summarized in table 3.

Between respective tests, the  $p_H$ , the total day output, the total night output and the six hour output test, of the diet groups significant differences occur more frequently than ninety-nine times in one hundred. To determine any effect on water balance due to retention of fluid because of diet, the total twenty-four hour output of urine is determined by the summation of the total day and the total night output. As is seen in table 3, there is no consequential difference in the means of the determinations of the twenty-four hour output.

Since it has been shown that the age of the patient and the duration of the disease have no effect on renal function as illustrated by the six tests considered, the results of the study of the patients with hypertension and the observations on normal subjects are divided into six groups each, according to the tests used. Thus the means and their standard deviation are computed, all ages and durations included with the use of the formulas for standard error.<sup>11</sup> The summary of this collation is recorded in table 4.

11. Fisher,<sup>6</sup> pp. 101-102.

TABLE 3.—*Comparison of the Effect of a General Diet and the Effect of an Alkaline Diet on the Renal Function of Patients with Hypertension*

Test		Diet	
		General Diet	Alkaline Diet
pH of urine	Mean.....	6.4	7.25
	Standard deviation of the mean	0.08	0.05
	Difference.....		0.65
	P.....		0.01 *
Total day output of urine	Mean.....	953.0 cc.	724.0 cc.
	Standard deviation of the mean	43.1	45.2
	Difference.....		229.0 cc.
	P.....		0.01 *
Total night output of urine	Mean.....	372.0 cc.	574.0 cc.
	Standard deviation of the mean	29.0	50.5
	Difference.....		202.0 cc.
	P.....		0.01 *
Six hour output of urine	Mean.....	688.0 cc.	497.0 cc.
	Standard deviation of the mean	33.6	47.0
	Difference.....		191.0 cc.
	P.....		0.01 *
Total twenty-four hour output of urine	Mean.....	1,319.2 cc.	1,299.2 cc.
	Standard deviation of the mean	48.6	55.1
	Difference.....		20.0 cc.
	P.....		0.8
Specific gravity difference	Mean.....	1.0149 Gm./cc.	1.0140 Gm./cc.
	Standard deviation of the mean	0.0007	0.0011
	Difference.....		0.0009 Gm./cc.
	P.....		0.615
Phenolsulfonphthalein excretion	Mean.....	53.0%	59.0%
	Standard deviation of the mean	2.0	2.7
	Difference.....		6.0%
	P.....		0.09

\* Any difference in means that is significant is indicated by a value for P of 0.01 or less.

TABLE 4.—*Renal Function in Grouped Patients with Essential Hypertension and Grouped Normal Subjects as Illustrated by the Results of Common Clinical Tests*

Test		Blood Pressure	
		Hypertensive	Normal
Total day output of urine	Mean.....	943.0 cc.	1,013.0 cc.
	Standard deviation of the mean	35.3	48.2
	Difference.....		70.0 cc.
	P.....		0.24
Total night output of urine	Mean.....	377.5 cc.	309.0 cc.
	Standard deviation of the mean	26.7	27.1
	Difference.....		68.5 cc.
	P.....		0.07
Six hour output of urine	Mean.....	700.0 cc.	772.0 cc.
	Standard deviation of the mean	30.2	41.0
	Difference.....		71.0 cc.
	P.....		0.15
Specific gravity difference	Mean.....	1.0163 Gm./cc.	1.0204 Gm./cc.
	Standard deviation of the mean	0.0006	0.0011
	Difference.....		0.0041 Gm./cc.
	P.....		0.01 *
Phenolsulfonphthalein excretion	Mean.....	55.5%	63.2%
	Standard deviation of the mean	1.685	2.28
	Difference.....		7.7%
	P.....		0.01 *
Urea clearance, percentage of normal urine	Mean.....	65.5	63.5
	Standard deviation of the mean	2.56	3.05
	Difference.....		2.2
	P.....		0.58

\* Any difference between means that is significant is indicated by values for P of 0.01 or less.



With the value for  $P$  less than 0.01 the differences between the hypertensive patients and the normal subjects in the fixation of specific gravity and the excretion of phenolsulfonphthalein are highly significant. Thus two of six determinations in this study offer a real difference between the renal function of a group of patients with essential hypertension and the renal operation of a group of normal subjects.

#### COMMENT

Although an adjunct rather than a mainstay of proof, statistical analysis is necessary in order more clearly to define the values at issue. Certain criticism of methods is valid. It is true that the numbers of samples in certain groups are small. Even so, an indication of a trend can be traced. It may be said that there is a violation in theory, at least, of the prerequisites of the random sample. Three major limitations to such sampling are unavoidable. All of these patients were hospitalized; all had dietary and therapeutic restrictions, and all had to have six tests performed during one hospitalization.

These statistical analyses and the subsequent results are made more easily understandable when it is emphasized that these results are from the study of a group of hypertensive patients and a group of normal subjects as groups and not from a comparison of the individuals forming each group. From a practical point of view the differences demonstrated here might not be elicited between any 2 individuals selected at random as representative of their respective groups. As such, these tests are not practical as clinical laboratory methods for demonstration of impairment of renal function in an isolated patient suspected of having essential hypertension, as may only be illustrated by computations derived from large numbers of hypertensive patients and normal subjects taken as groups.

From the study of the first and the second variable, there is little doubt that within the limits of these tests there is evidence that the age of a subject and the duration of hypertension have no effect on concentration or excretion by the kidney, either in patients with hypertension or in normal persons.

With an increase of diastolic pressures to extremes there coexists a caducous excretion of phenolsulfonphthalein. A decrease in the six hour output of urine may possibly be present, indicating an increase in renal impairment in patients with excessive diastolic pressures, although such changes in function may be due to a delay in excretion of urine.

At the time when alkaline diet was used extensively in the treatment of patients with essential hypertension the only check on the effects of this diet was the  $p_H$  of the urine. Although the only change in the management of some of our patients was the substitution of an alkaline

diet, it is a just criticism<sup>12</sup> that the variation in the excretion of the urine noted in the studies on alkaline diet cannot be proved to be due to the alkalinity of a patient as controlled by the diet. However, at the time the alkaline diet was used, the patients had a definite variation in renal excretion from those patients on the general diet. The fixation of the specific gravity was the same in both groups. Although there is no apparent retention of fluid in the tissues of hypertensive patients using the alkaline diet, as indicated by the equivalent volumes in the twenty-four hour output of urine of the two groups, there is a definite delay in excretion of urine, as is seen in the reduction of the six hour output and the total day output, with the compensatory increase in the night output.

In collecting the results of tests on patients in all decades according to the tests performed in the study summarized in table 4, one can note definite differences between two of the renal function tests in groups of patients with essential hypertension and groups of normal subjects. There is evidence of fixation of the specific gravity of the urine which with the reduction in ability to excrete phenolsulfonphthalein, is evidence of impairment of the function of the kidney in patients with essential hypertension. In the presence of the fixation of the specific gravity there is no increase in the volume output of the urine, which is the usual compensatory action in other types of renal disease with specific gravity fixation.<sup>13</sup> Although definite, the difference between the means in the specific gravity tests is not great. This in itself is a possible explanation of the lack of variation from normal of the rate and the time of urine output. The reduction in excretion of phenolsulfonphthalein must be due to delay in glomerular filtration. There is no variation in fluid loss due to insensible perspiration in the absence of sweat in circulatory disease.<sup>14</sup>

#### SUMMARY

Instead of studying differences between single examples and noting variations between two random single samples, a more sensitive observation is made by comparing the results of renal function tests on patients with essential hypertension as a group with results of the same tests on normal subjects as a group.

Working even in this manner we find that there is no variation of the renal function from the normal in a patient with essential hypertension because of the age of the patient or because of the duration of the disease.

12. Lucia, S. P.: Personal communication to the authors.

13. Lashmet, F. H., and Newburgh, J. H.: A Comparative Study of the Excretion of Water and Solids by Normal and Abnormal Kidneys, *J. Clin. Investigation* **11**:1003-1010, 1932.

14. Dubois, E. F.: *Basal Metabolism in Health and Disease*, ed. 3, Philadelphia, Lea & Febiger, 1936, p. 446.

There is a retardation of the flow of urine in patients with hypertension having high diastolic pressures.

There is some indication of retardation of urinary flow and compensatory nocturia in hypertensive patients on an alkaline diet.

In general, there is fixation of specific gravity and retardation of phenolsulfonphthalein output in patients with hypertension.

The Volhard concentration and the phenolsulfonphthalein excretion test themselves are of no use clinically for the differential diagnostic purpose of distinguishing between persons with essential hypertension and normal persons in isolated instances. These studies indicate variation in the physiologic processes of the kidney due to a disease process coexistent with essential hypertension.

Dr. A. J. Lotka and Dr. N. R. Blatherwick of the Metropolitan Life Insurance Company assisted us and criticized our statistical methods. They expressed the belief that the conclusions drawn are essentially justifiable. All calculations have been checked and conclusions verified by H. H. Ritchie, Chairman, Department of Mathematics, Santa Barbara Junior High School. Dr. Fritz Bischoff, Chairman, Department of Research, Santa Barbara Cottage Hospital, offered criticism and assisted us in our analysis.

All computations are on file in the Department of Research, Santa Barbara Cottage Hospital. They are available for the use of other investigators for comparison or as an adjunct to their work.

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# EFFECT OF ULCER ON ACIDITY AND NEUTRALIZING ABILITY IN DUODENAL BULB

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The preponderance of the investigation dealing with the pathogenesis and the maintenance of chronic duodenal ulcer has been concerned with the acid gastric juice. A large amount of work has been reported tending to incriminate this factor and designed to determine the best means of combating and alleviating its ill effects. As a consequence, clinical attention has been narrowly focused on the acidity in the stomach, while the acidity in the duodenum has been almost entirely neglected. In order to evaluate adequately the role of the acid gastric juice in duodenal ulcer, it is essential to know what effect the acid chyme has on the reaction and the neutralizing ability at the actual site of the ulcer—the duodenal bulb.

The contents of the first part of the duodenum in normal persons have been shown to possess an ability to neutralize, buffer and dilute gastric chyme which is generally very efficient.<sup>1</sup> In contradistinction to normal subjects, however, most patients with duodenal ulcer exhibit gastric hyperacidity and hypersecretion.<sup>2</sup> It is problematic whether a

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Aided by a grant from John Wyeth and Bro., Inc.

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Portion of thesis submitted by Dr. Berk to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Medical Science (D.Sc. [Med.]) for graduate work in internal medicine.

1. Berk, J. E.; Rehfuß, M. E., and Thomas, J. E.: The Acidity of the "Ulcer-Bearing Area" of the Duodenum in Normal Persons, *Am. J. Digest. Dis.* 9:276, 1942.

2. (a) Alvarez, W. C.: Standards of Normal in Gastric Secretion, *Ann. Int. Med.* 6:315, 1932. (b) Bloomfield, A. L.: Clinical Aspects of Gastric Secretion, *ibid.* 6:307, 1932; (c) The Problem of Gastric Hyperacidity, *Am. J. Digest. Dis.* 6:700, 1939. (d) Bloomfield, A. L., and Polland, W. S.: The Diagnostic Value of Studies of Gastric Secretion, *J. A. M. A.* 92:1508 (May 4) 1929. (e) Bloomfield, A. L.; Chen, C. K., and French, L. R.: Basal Gastric Secretion as a

(Footnote continued on next page)

patient with ulcer with a scarred, contracted, irritable duodenal cap into which there is being emptied excessive amounts of acid gastric juice displays a similar neutralizing efficiency. On the answer to this question rests in part some insight into the physiologic defects in ulcer; only through its answer can the acid factor in duodenal ulcer be properly evaluated.

Several investigators have endeavored to determine the duodenal reaction in patients with duodenal ulcer,<sup>3</sup> but Morton alone<sup>4</sup> concerned himself with the important "ulcer-bearing" duodenal cap. Patients with peptic ulcer, he found, displayed higher values and wider variations in duodenal bulb acidity than did normal persons. The most constant feature in the patients with ulcer was the more or less uniform presence of titratable free acid in the contents of the first part of the duodenum.

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Clinical Test of Gastric Function with Special Reference to Peptic Ulcer, *J. Clin. Investigation* **19**:863, 1940. (f) Bockus, H. L.; Glassmire, C., and Bank, J.: Fractional Gastric Analysis in Two Hundred Cases of Duodenal Ulcer, *Am. J. Surg.* **12**:6, 1931. (g) Cheney, G., and Bloomfield, A. L.: Gastric Function in Cases of Gastric and Duodenal Ulcer, *J. Clin. Investigation* **5**:511, 1928. (h) Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine in the Presence of Various Types of Gastric and Duodenal Lesions, *J. A. M. A.* **97**:1141 (Oct. 17) 1931. (i) Hurst, A. F.: Hyperesthenic Gastric Diathesis, *Lancet* **2**:1369, 1922. (j) Hurst, A. F., and Venables, J. F.: The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, *Guy's Hosp. Rep.* **79**:249, 1929. (k) Pollard, W. S.: Histamine Test Meals: An Analysis of Nine Hundred and Eighty-Eight Consecutive Tests, *Arch. Int. Med.* **51**:903 (June) 1933. (l) Rehfuess, M. E.: Possibilities of Fractional Gastric Analysis, *J. A. M. A.* **71**:1534 (Nov. 9) 1918; (m) *The Diagnosis and Treatment of Diseases of the Stomach*, Philadelphia, W. B. Saunders Company, 1927. (n) Ruffin, J. M., and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2,877 Gastric Analyses, *Ann. Int. Med.* **12**:1940, 1939. (o) Vanzant, F. R.; Osterberg, A. E.; Alvarez, W. C., and Rivers, A. B.: Studies of Gastric Pepsin: II. Secretion of Pepsin in Cases of Duodenal Ulcer and Pseudo-Ulcer, *J. Clin. Investigation* **12**:557, 1933. (p) Vanzant, F. R.; Alvarez, W. C.; Berkson, J., and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with the Help of a New and Accurate Technic, *Arch. Int. Med.* **52**:616 (Oct.) 1933.

3. (a) Einhorn, M.: Experiences with the Duodenal Contents, *J. A. M. A.* **55**:6 (July 2) 1910; (b) Fractional Examination of the Duodenal Contents in Peptic Ulcer, *ibid.* **72**:1471 (Nov. 5) 1921; (c) *The Duodenal Tube and Its Possibilities*, Philadelphia, F. A. Davis Company, 1926. (d) Einhorn, M., and Rosenbloom, J.: A Study of the Duodenal Contents in Man, *Arch. Int. Med.* **6**:666 (Dec.) 1910. (e) Kearney, R. W.; Comfort, M. W., and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study, *J. Clin. Investigation* **20**:221, 1941. (f) Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, *Am. J. M. Sc.* **177**:65, 1929; (g) Observations on Peptic Ulcer, *South. Surgeon* **3**:316, 1934.

4. Morton, footnotes 3 f and g.

Morton's work, however, has several shortcomings; there was uncertainty as to the precise position of the tip of the duodenal tube throughout the period of observation, for the most part only single samples were removed and  $p_H$  determinations were not made.

The present communication represents the results of an inquiry into the acidity and the neutralizing ability of the duodenal bulb contents in patients with duodenal ulcer through the use of a method which largely meets the objections raised to previous investigations.<sup>5</sup> It was hoped that the information gained would contribute to a solution of some of the problems which have been posed and would provide better criteria with which to judge the role of the acid gastric juice in duodenal ulcer.

#### MATERIAL

From the wards and from the outpatient gastrointestinal disease clinic of the Jefferson Hospital 19 patients were chosen at random, all of whom at the time were complaining of symptoms referable to an ulcer and all of whom gave radiologic evidence of an active, nonobstructive duodenal ulcer without any demonstrable lesion in the stomach. A number had had previous episodes of bleeding, and in the few who had been subjected to gastroscopic examination no evidence of gastritis or gastric ulcer was found.

Of the entire group studied 17 persons (12 men, 5 women) were selected for the purpose of this presentation because the experiments performed on them were considered satisfactory from the technical viewpoint. The 17 ranged in age from 21 to 59 years, with an average age of 42.7 years. The men ranged from 21 to 57 years of age, with an average of 42.5 years, and the women from 21 to 59 years of age, with an average of 43.2 years.

#### METHOD

Each patient was studied in the morning before breakfast and after a twelve hour fast. Through the use of a specially constructed double lumen tube and a method which permitted more or less constant fluoroscopic control as well as roentgenographic proof of the position of the tube,<sup>5</sup> specimens were simultaneously withdrawn at ten minute intervals from the pyloric antrum and from the duodenal cap. Samples were collected for one-half hour in the fasting state and for two hours after the feeding of an Ewald meal consisting of two pieces of stale bread or dry toast and 250 cc. of tap water.

On each gastric and duodenal sample the  $p_H$  was determined at once through the use of a Leeds-Northrup  $p_H$  indicator, which employs a glass electrode. The free and the total acidity of each specimen was titrimetrically estimated after filtration, Toepfer's reagent and phenolphthalein being used as the respective color indicators.<sup>6</sup> On each duodenal sample, in addition, there was determined what was called the excess neutralizing ability. This consisted of the amount of

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5. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and First Part of the Duodenum, *J. A. M. A.* **119**:259 (May 16) 1942.

6. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: Limitations in the Use of Color Indicators in Gastric Analysis, *Am. J. Digest. Dis.* **9**:106, 1942.

tenth-normal hydrochloric acid which it was necessary to add before Toepfer's reagent indicated a positive reaction for free acid.<sup>7</sup>

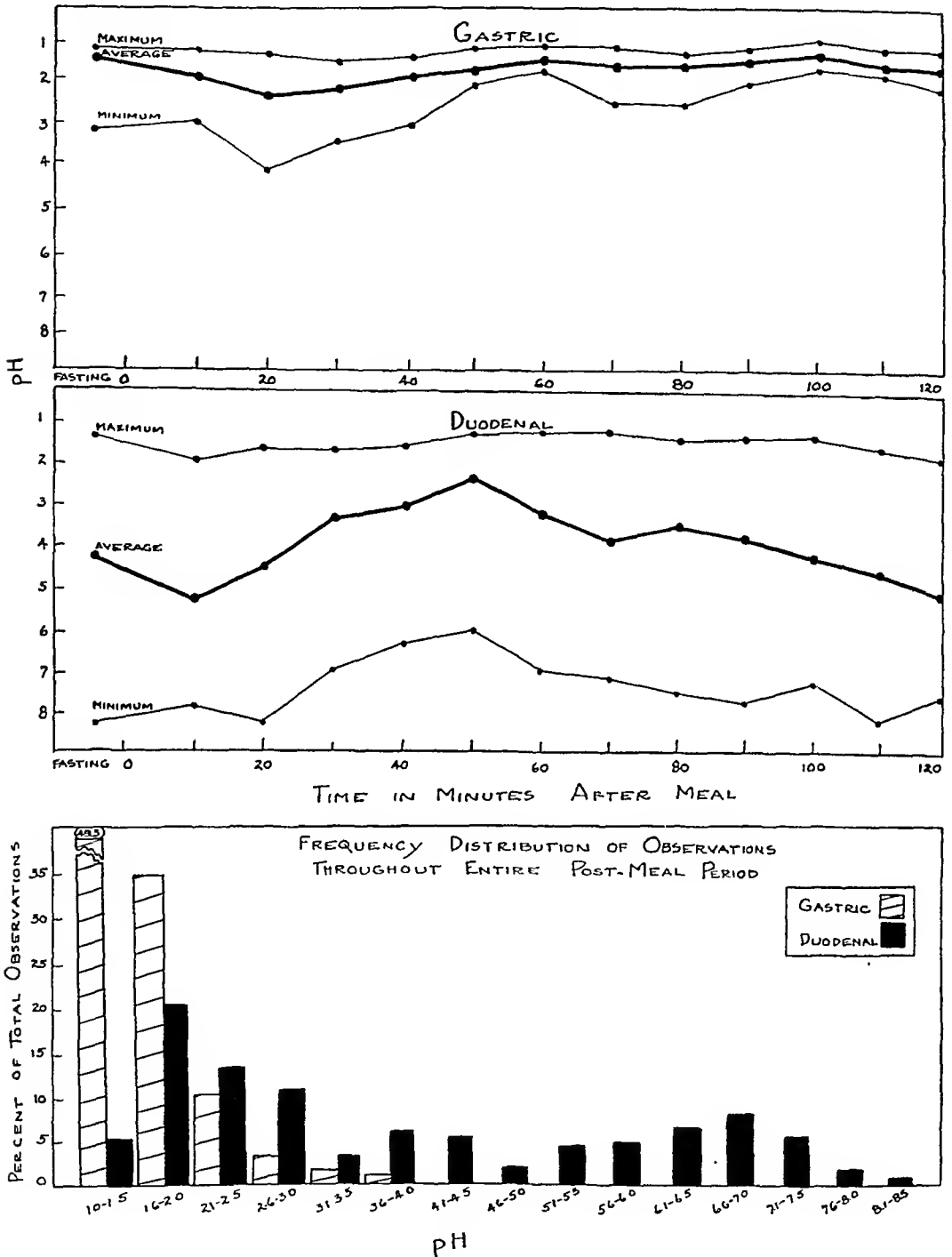


Chart 1.—Acidity in  $p_H$  units of samples collected simultaneously from just above and just below the pylorus.

7. Berk, J. E.; Thomas, J. E., and Reh fuss, M. E.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, *Am. J. Physiol.* **136**:157, 1942; footnote 5.

Of the 32 experiments which were made 23 were accepted as satisfactory from the standpoint of technic. These involved 2,202 separate determinations consisting of 633 determinations of  $p_H$ , 625 estimations of free acid, 625 estimations of total acidity and 319 determinations of excess neutralizing ability of the duodenal contents. The values for the four specimens obtained from each person in the fasting state were averaged and expressed as a single value.

## RESULTS

*Acidity in  $p_H$  Units (chart 1).*—Stomach: As was to be expected, the hydrogen ion concentration of the stomach contents in patients with duodenal ulcer was much greater than that encountered in normal persons (an average postmeal  $p_H$  of 1.68, as compared with 2.78).<sup>1</sup> Not only was the average  $p_H$  lower, but the distribution range of the values was much narrower. Only 2 (0.88 per cent) of the 227 postmeal samples exhibited a  $p_H$  in excess of 3.5, the value which we had adopted as the critical one for free acid.<sup>6</sup>

Duodenum: The average postmeal duodenal  $p_H$  was also lower than that observed in normal persons (3.87, as compared with 4.94).<sup>1</sup> Although numerically the differences from the normal  $p_H$  in the stomach and in the duodenum of patients with ulcer were approximately equal, on a percentage basis the gastric  $p_H$  was 39.4 per cent, while the duodenal  $p_H$  was only 21.6 per cent, lower than the normal value. This fact strongly suggests that the reaction in the duodenal cap is only in part determined by the hydrogen ion concentration of the stomach contents and that increases in gastric acidity are not necessarily associated with equal increases in duodenal acidity.

Samples collected simultaneously from just above and just below the pylorus in patients with ulcer exhibited a consistent difference in  $p_H$ , just as did samples from normal persons. Surprisingly enough, the difference in the average postmeal value was as great (2.19  $p_H$  units) as that displayed by normal persons (2.17  $p_H$  units). In contradistinction to normal persons, in patients with ulcer the average postmeal  $p_H$  of the duodenal bulb contents not only fell below 3.5 but remained below this critical level for four consecutive readings (thirty to sixty minutes postcibal, inclusive). Furthermore, 53.9 per cent of all the post-Ewald-meal samples had positive reactions for free acid ( $p_H$  3.5 or below), an increase of 70 per cent over the samples from normal persons fed the same meal.

A pronounced fluctuation in the reaction of the contents of the duodenum, especially in the first part, has been noted both in dogs<sup>8</sup>

8. Mann, F. C., and Bollman, J. L.: A Symposium Concerned with the Duodenal Factors in the Neutralization of Acid Chyme, *Am. J. Digest. Dis. & Nutrition* 2:284, 1935.



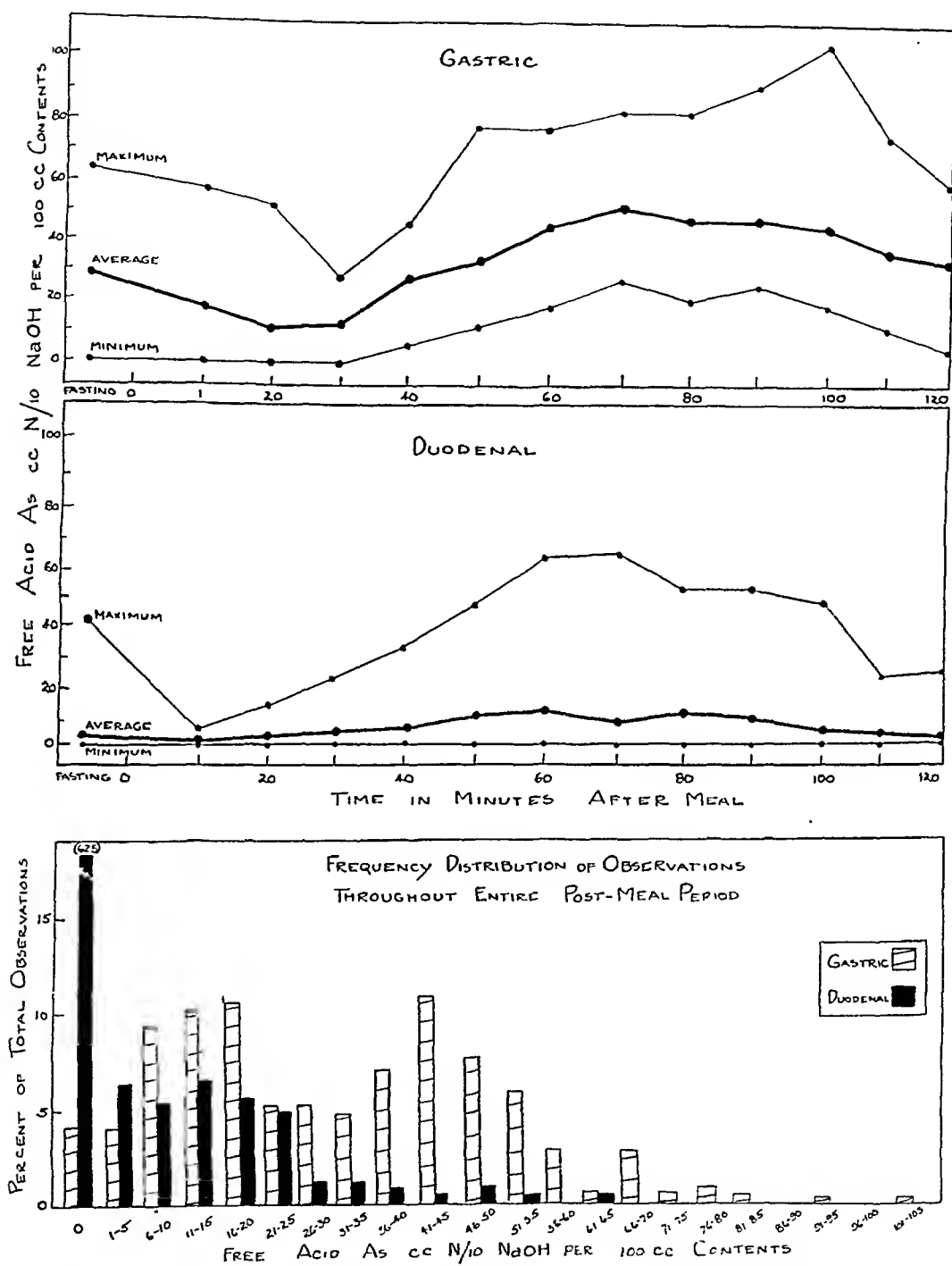


Chart 2.—Free acid as determined on samples collected simultaneously from just above and just below the pylorus.

and in man.<sup>9</sup> We did not observe this fluctuation in normal subjects, but a considerable degree of fluctuation in  $p_H$  readings was by no means uncommon in patients with duodenal ulcer. As a consequence, low  $p_H$  values were widely scattered throughout the various postmeal intervals, although most of the low readings tended to concentrate between the thirty and the seventy minute determinations.

The discrepancy in the configuration of the plotted values of the average  $p_H$  in the pyloric antrum and in the duodenal cap is worthy of special note. The relative independence of these curves shows that one cannot rely with any assurance on the gastric  $p_H$  as an index of the behavior of the  $p_H$  present over the same period of time in the first part of the duodenum.

*Free Acid (chart 2).*—Stomach: The distinct curve pattern of the plotted values for average gastric free acid was in sharp contrast to the relatively flat line assumed by the plotted values for average gastric  $p_H$  (chart 1). The pattern more closely simulated that of the average duodenal  $p_H$  (chart 1), yet a definite variation can be discerned.

Duodenum: Free acid as determined colorimetrically was found in the contents of the first part of the duodenum in 37.5 per cent of all the postmeal specimens. This frequency was much greater than that for normal persons.<sup>1</sup> In the colorimetric determinations of free acid our end point with Toepfer's reagent was just below  $p_H$  3.5.<sup>6</sup> With our technic, however, the filtration and the dilution of the samples preparatory to titration introduce an error that results in some false negative readings.<sup>6</sup> We must assume, therefore, that all specimens with a  $p_H$  of 3.5 or less in the unfiltered and undiluted state contain free acid. On this basis over one half (53.9 per cent) of all the postmeal duodenal samples contained free acid; the corresponding value for normal subjects determined in the same way was slightly less than one third (31.7 per cent).

Colorimetrically 82.3 per cent and electrometrically 100 per cent of all the patients showed free acid in their duodenal bulb contents at some time during the postmeal phase. Colorimetrically 52.9 per cent and electrometrically 70.5 per cent of the patients showed free acid in three or more consecutive postmeal samples. These figures are much greater than similar ones determined for normal subjects.<sup>1</sup> Furthermore, free acid tended to persist for longer periods in the duodenum in patients with ulcer than in normal subjects; there was much less of a tendency toward rapid recuperation of neutralizing efficiency. This observation

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9. Eyerly, J. B.: Comparative  $p_H$  Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy, *Am. J. Digest. Dis.* **7**:431, 1940. Karr, W. G., and Abbott, W. O.: Intubation Studies of the Human Small Intestine: IV. Chemical Characteristics of the Intestinal Contents in the Fasting State and as Influenced by the Administration of Acids, of Alkalies and of Water, *J. Clin. Investigation* **14**:893, 1935. Kearney, Comfort and Osterberg.<sup>3e</sup>

is best illustrated by the fact that one half (52.9 per cent) of all the patients studied showed  $p_H$  values of 3.5 or less for six consecutive postmeal samples.

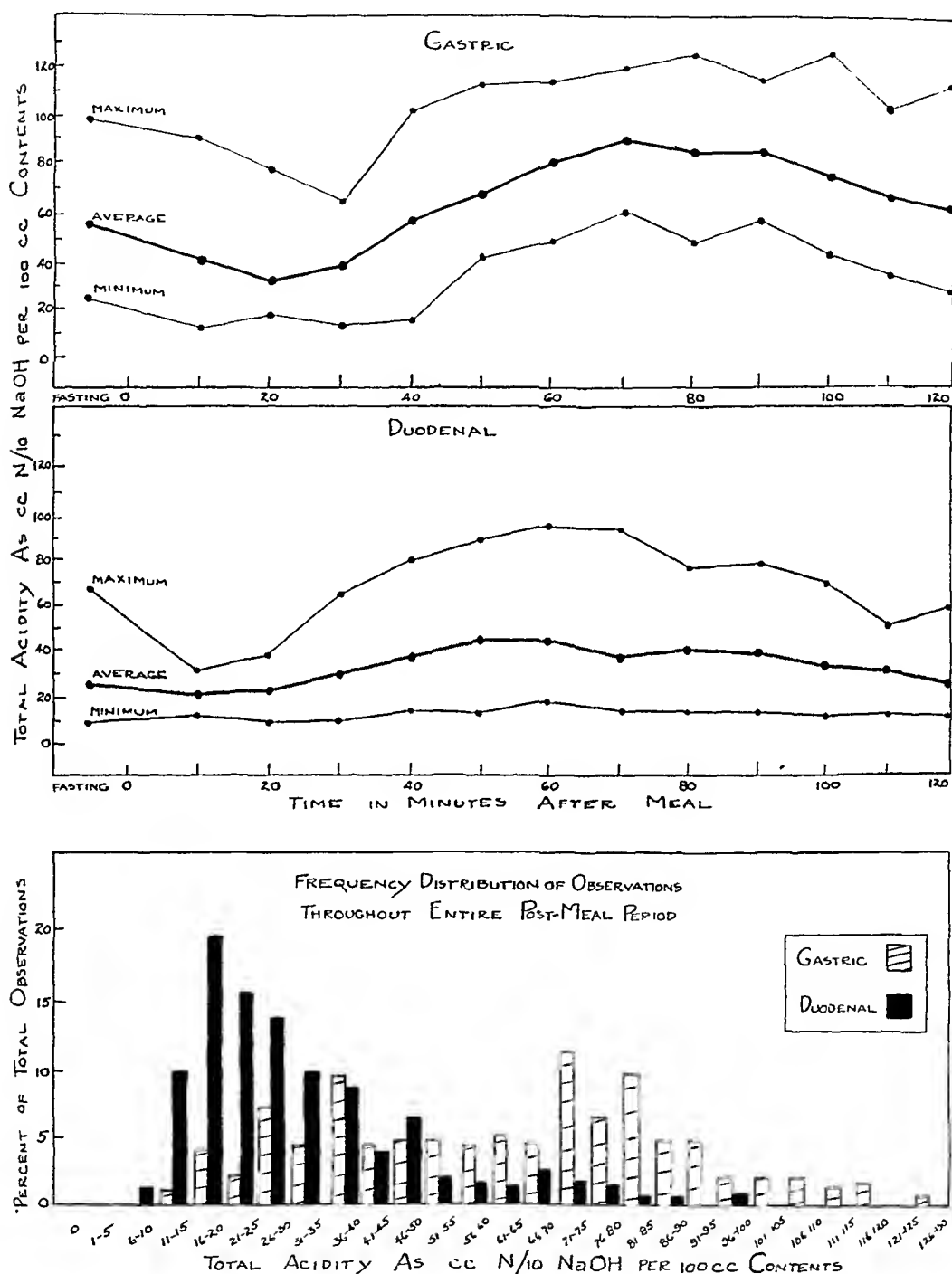


Chart 3.—Total acidity of samples collected simultaneously from just above and just below the pylorus.

*Total Acidity (chart 3).—Stomach:* The average gastric total acidity, like the free acid, was sharply different in curve pattern from

the average gastric  $p_H$  (chart 1). Even though the pattern bore a closer resemblance to the curve of the average duodenal  $p_H$  (chart 1), the parallelism was not close enough at all points to warrant reliance on gastric total acidity as a sure index of the behavior of the coexistent effective acidity in the duodenal bulb.

Duodenum: The lack of sharp agreement between the curve for average gastric and that for average duodenal total acidity should be

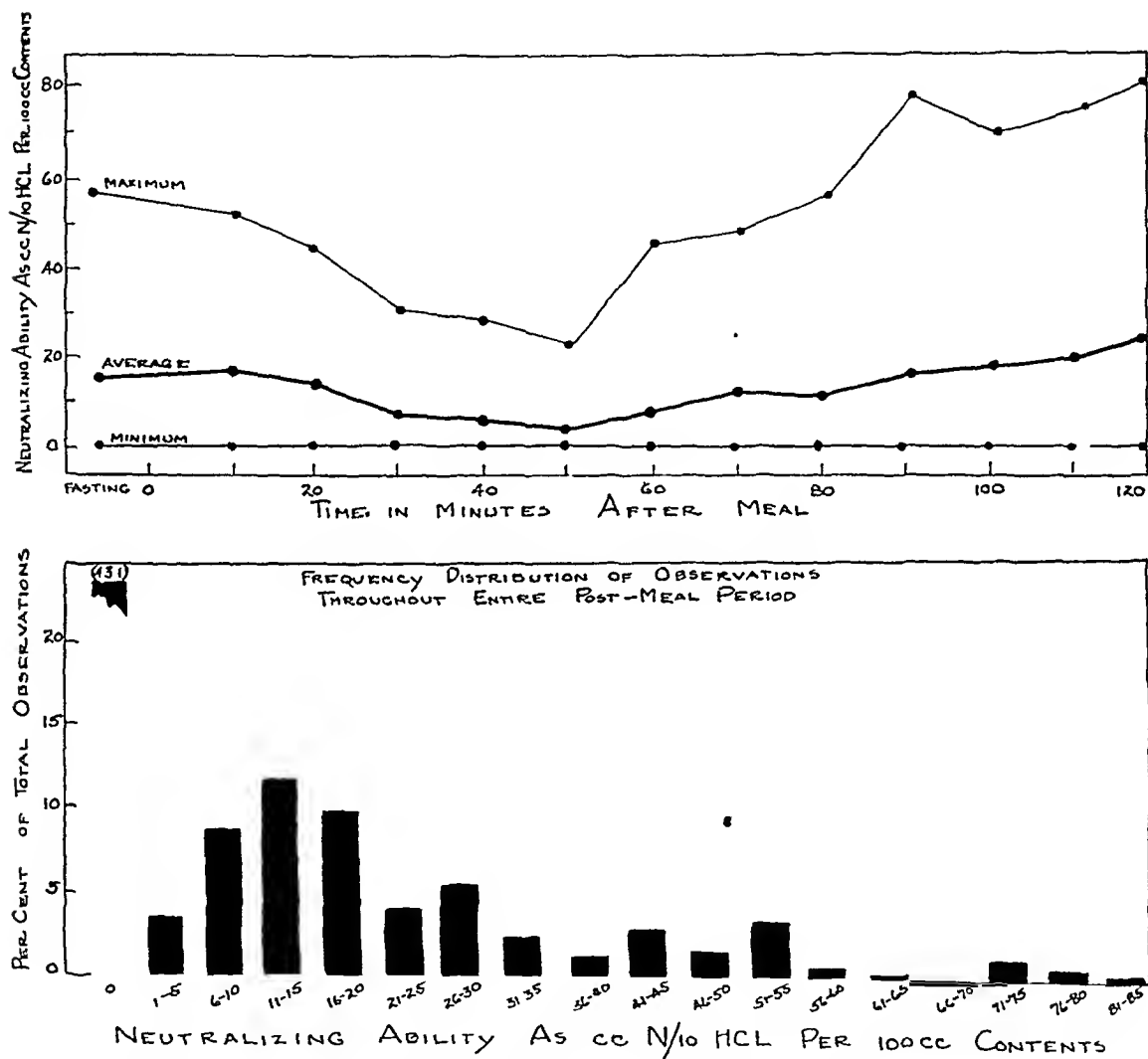


Chart 4.—Excess neutralizing ability of the contents of the first part of the duodenum.

noted. The slight but significant discrepancies between them is further indication of the absence of a constant relationship between the acidity simultaneously determined in the stomach and in the duodenal contents.

*Excess Neutralizing Ability of the Duodenal Contents (chart 4).—*Excess neutralizing ability has been defined<sup>7</sup> as a measure of the reserve capacity which the contents of the duodenal bulb possess to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content.

More than two out of every five (43.1 per cent) of the postmeal duodenal samples failed to display any excess neutralizing ability as compared with less than one in every five (19.9 per cent) of the specimens obtained from normal subjects.<sup>1</sup> In added contrast to normal persons, however, patients with ulcer showed a much wider distribution range of values. It is a physiologic maxim that efficient regulatory mechanisms show narrow ranges. Wide departures from the average, therefore, as illustrated on the one hand by the greater number of specimens containing free acid or on the other by the higher range of values for excess neutralizing ability, are indicative of inefficiency of the duodenal neutralizing regulatory mechanism in patients with ulcer.

The rise in the value for average excess neutralizing ability during the second postprandial hour, when the values for gastric acidity were high, probably accounts for the concomitant increase in duodenal  $p_H$  and suggests that the duodenal neutralizing capacity was in the ascendency during that period.

#### COMMENT

There are recognized deficiencies in the method of study employed which permit a fair amount of experimental error.<sup>5</sup> Our primary purpose in this presentation, however, was to compare patients with duodenal ulcer with normal persons in regard to the acidity and the neutralizing ability of the contents of the first part of the duodenum. The utilization, therefore, of the same method of study for the two groups affords an acceptable means of comparison, because any inherent experimental error is thereby equally applicable to each group.

The duodenal bulb is distinctly an acid area, especially in patients with duodenal ulcer. Its contents in such patients after an Ewald meal have an average  $p_H$  of about 3.9. This value indicates a hydrogen ion concentration in excess of that encountered in normal persons; still, it is above the critical level below which free acid is said to be present ( $p_H$  3.5).

The ability of the contents of the first part of the duodenum to neutralize, buffer and dilute the gastric chyme is in evidence in patients with duodenal ulcer although impaired. Despite higher average values for gastric acidity, patients with duodenal ulcer are able to maintain an average difference in  $p_H$  between the contents of the pyloric antrum and the contents of the duodenal bulb which is as great as that in normal subjects. Nevertheless, as is best illustrated in the individual experiments, the neutralizing ability of the duodenal bulb in contrast to that of normal persons is overcome more frequently, to a greater extent and for longer periods of time. Electrometrically all the patients studied showed free acid ( $p_H$  3.5 or less) in the duodenal bulb contents at some time during a two hour fractional period of observation after an Ewald meal; over one half of them displayed a positive reaction for free acid in six consecutive postmeal samples. The increased frequency

with which free acid is encountered in the contents of the first part of the duodenum, as well as the higher average acidity values, for patients with ulcer as compared with those for normal subjects confirms Morton's <sup>4</sup> findings.

The explanation for the increase in duodenal acidity in patients with duodenal ulcer would appear, offhand, to rest in the higher values for gastric acidity which they display. Earlier investigators, however, have called attention to an apparent lack of relationship between gastric acidity and duodenal acidity,<sup>10</sup> and we <sup>1</sup> have been able to demonstrate that in normal persons the duodenal reaction is affected to a lesser extent than would be expected from an increase in gastric hydrogen ion concentration. In the present study also there was some indication that increases in gastric acidity in patients with duodenal ulcer are not necessarily associated with increases in duodenal acidity of equal magnitude (chart 1). Hence, in regard to evaluation of the acid factor in duodenal ulcer, it becomes a matter of some importance whether or not the acidity at the site of the ulcer proper is determined only by the degree of acidity of the gastric chyme.

We undertook to answer this question in part by comparing the entire group of patients with duodenal ulcer available for study with 6 normal subjects specially selected because of their high values for gastric acidity (charts 5, 6, 7 and 8). The close parallelism between the acid titers in the two groups is easily apparent. It is noteworthy, however, that the normal subjects, particularly in the second half of the observation period, uniformly displayed higher gastric acid concentrations and at the same time lower duodenal acid concentrations than did the patients with duodenal ulcer. This, we hold, is evidence that the degree of acidity of the stomach contents is by no means the sole determinant of the degree of acidity of the duodenal bulb contents and that patients with duodenal ulcer differ from normal persons not only in the direction of gastric hyperacidity but in the direction of a defectiveness of the neutralizing capacity in the duodenal bulb. The sharp fluctuation in the reaction of the contents of the first part of the duodenum

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10. The Fractional Examination of the Duodenal Contents, *Am. J. M. Sc.* **156**: 817, 1918. Friedenwald, J., and Sindler, J.: Fractional Analysis of the Duodenal Contents in Normal Individuals, *J. A. M. A.* **77**:1469 (Nov. 5) 1921. McClure, C. W., and Wetmore, A. S.: Studies in Pancreatic Function: Enzyme Concentration of Duodenal Contents After the Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men, *Boston M. & S. J.* **187**:882, 1922. McClure, C. W.; Wetmore, A. S., and Reynolds, S.: Physical Characters and Enzymatic Activities of Duodenal Contents: Findings During Gastric Digestion in Normal Young Men, *J. A. M. A.* **77**:1468 (Nov. 5) 1921. Okoda, S., and Arai, M.: The Hydrogen Ion Concentration of the Intestinal Contents, *J. Biol. Chem.* **51**:135, 1922. Einhorn.<sup>3b</sup> Einhorn.<sup>3c</sup> Kearney, Comfort and Osterberg.<sup>3e</sup> Morton.<sup>3f</sup>

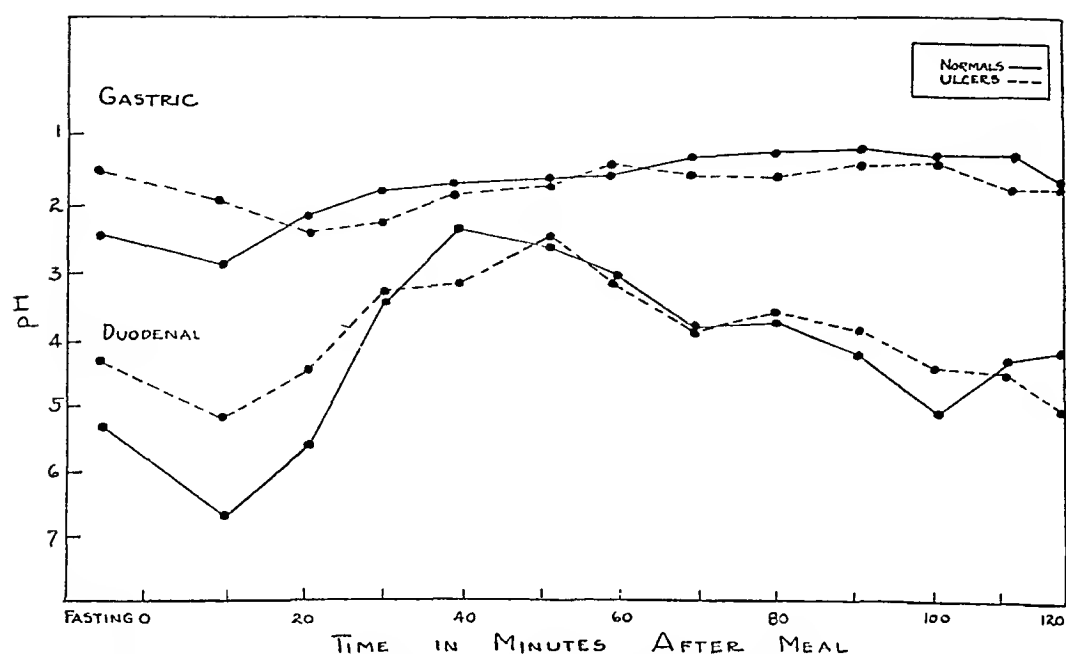


Chart 5.—Average acidity in  $pH$  units of samples collected simultaneously from just above and just below the pylorus from patients with duodenal ulcer compared with that of samples from a group of normal subjects with gastric hyperacidity.

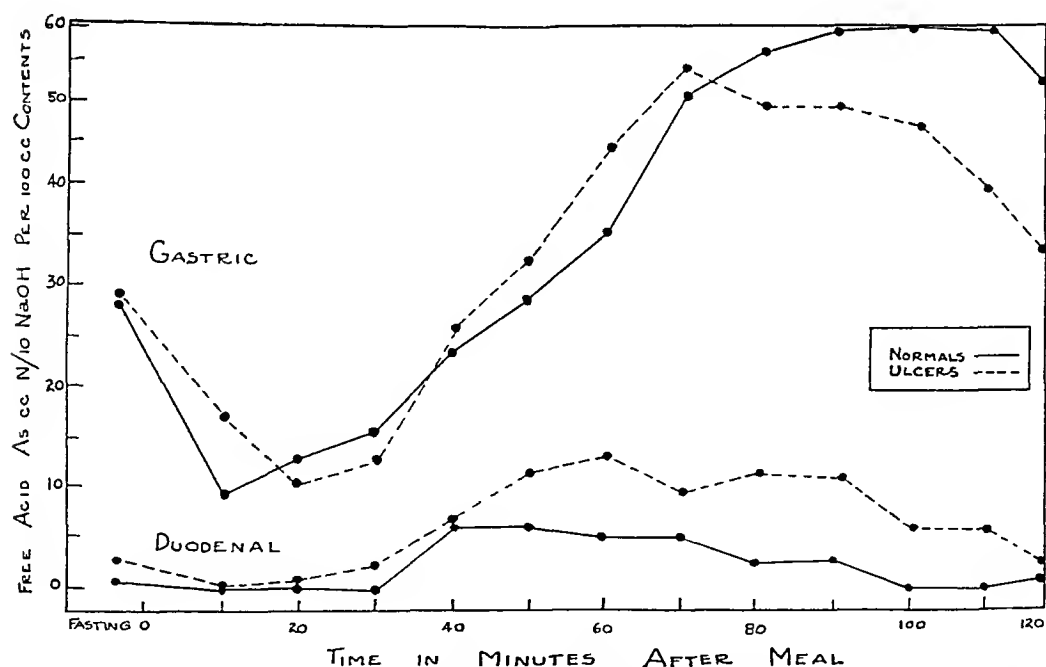


Chart 6.—Average free acid, as determined on samples collected simultaneously from just above and just below the pylorus of patients with duodenal ulcer compared with that of a group of normal subjects with gastric hyperacidity.

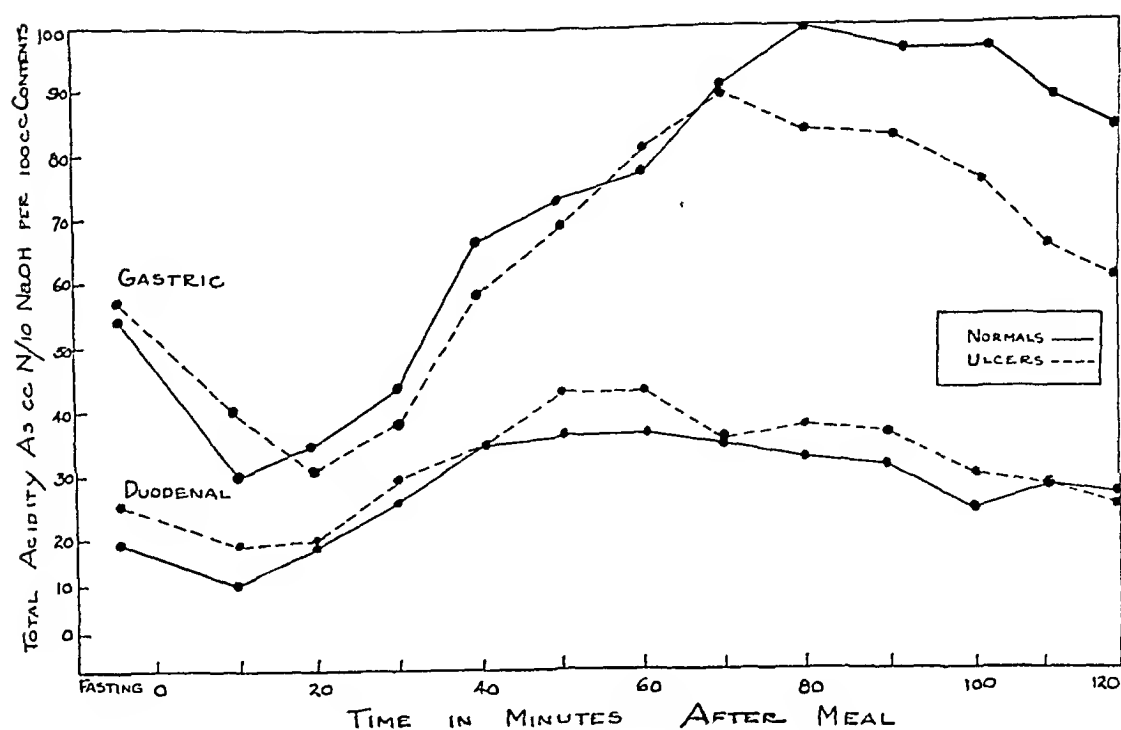


Chart 7.—Average total acidity of samples collected simultaneously from just above and just below the pylorus from patients with duodenal ulcer compared with that of samples collected from a group of normal subjects with gastric hyperacidity.

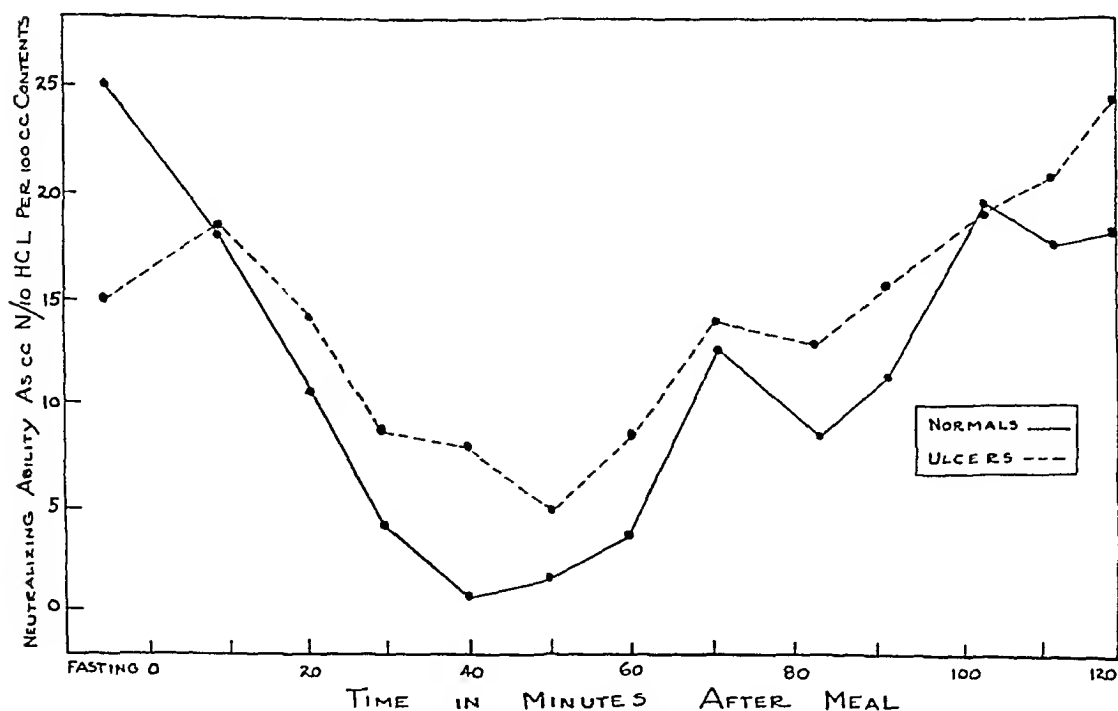


Chart 8.—Average excess neutralizing ability of the contents of the first part of the duodenum in patients with duodenal ulcer compared with that for a group of normal subjects with gastric hyperacidity.



which was noted in patients with ulcer but not in normal subjects (chart 1) is probably another manifestation of a defective neutralizing mechanism.<sup>3c</sup> In this respect, too, it is of interest that the average excess neutralizing ability of the duodenal contents (chart 8) was less in normal persons than in patients with ulcer. This fact, we assume, is attributable to a more efficient regulatory mechanism, which prevents wide excursions from the average in the direction either of excess acidity or of excess neutralizing ability.

It is to be emphasized that the conclusions we have drawn are all predicated on studies made on the acid concentration and not on the volume of gastric and duodenal contents. We have every reason to believe that the normal persons we selected were as much persons with hypersecretion as were the patients with duodenal ulcer, but with our method of study it was impossible to measure total amounts of acid without seriously interfering with normal physiologic processes.

The findings reported in this study are merely another small link in a growing chain of evidence indicating that the acid gastric juice per se is not so important a factor in ulcer as it has hitherto been considered. It is common knowledge that normal persons may have values for gastric acid just as high as patients with duodenal ulcer,<sup>11</sup> and it is just as well recognized that there is no reduction in gastric acidity with the healing of an uncomplicated duodenal ulcer.<sup>12</sup> Bloomfield and French<sup>12b</sup> could demonstrate no constant relationship between the basal gastric acidity and the speed of healing of an ulcer. Alvarez<sup>12a</sup> found no certain relationship between the acid titer and the intractability of an ulcer. Brown and Dolkart<sup>12c</sup> concluded that the trend of gastric acidity bears no relationship to the onset of a recurrence in patients with ulcer. Prolonged gastric hypersecretion in dogs has failed according to

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11. Baird, M. M.; Campbell, J. M. H., and Hern, J. R. B.: Gastric Secretion, Physique and Physical Fitness, *Guy's Hosp. Rep.* **74**:339, 1924. Bennett, T. I., and Ryle, J. A.: Studies in Gastric Secretion: V. A Study of the Normal Gastric Function Based on the Investigation of One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, *ibid.* **71**:286, 1921. Polland, W. S., and Bloomfield, A. L.: Normal Standards of Gastric Function, *J. Clin. Investigation* **9**:651, 1931. Bloomfield.<sup>2b</sup> Bloomfield and Polland.<sup>2d</sup> Hurst.<sup>2f</sup> Rehfuess.<sup>21</sup>

12. (a) Alvarez, W. C.: The Unreliability of Gastric Analysis as an Index to Prognosis in Cases of Peptic Ulcer, editorial, *Am. J. Digest. Dis.* **6**:557, 1939. (b) Bloomfield, A. L., and French, L. R.: Basal Gastric Secretion in Cases of Peptic Ulcer: Relation of Acidity to Healing of Ulcer, *J. Clin. Investigation* **17**:667, 1938. (c) Brown, C. F. G., and Dolkart, R. E.: Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, *Arch. Int. Med.* **60**:680 (Oct.) 1937. (d) Sandweiss, D. J.; Sugarman, M. H.; Friedman, M. H. F.; Saltzstein, H. C., and Farbman, A. A.: The Effect of Urine Extracts on Peptic Ulcer: An Experimental and Clinical Study, *Am. J. Digest. Dis.* **8**:371, 1941. (e) Bockus, Glassmire and Bank.<sup>2f</sup> (f) Hurst and Venables.<sup>2j</sup>

some investigators,<sup>13</sup> to produce chronic gastric or duodenal ulcer, and we were able to demonstrate that even though temporary gastric hypersecretion in normal dogs frequently interferes with adequate neutralization in the duodenal bulb, the impairment is usually slight and for the most part is rapidly corrected.<sup>14</sup> What well might prove to be the death knell of the theory of the acid factor in ulcer is the recent work with urogastrone. This has shown rather conclusively that the urine of patients with symptoms of active duodenal ulcer contains a gastric secretory depressant<sup>15</sup> and, what is even more striking, that normal urine contains a substance having a definite prophylactic and therapeutic effect against Mann-Williamson ulcers and causing symptomatic improvement in patients with duodenal ulcer without bringing about any decrease in the gastric secretory response to stimuli.<sup>12d</sup>

There is much to corroborate the suggestive evidence we have gathered that a primary defect in duodenal ulcer is an impaired efficiency of duodenal neutralization. Resistance to the formation of an experimental ulcer has been shown to decrease in proportion to an interference with the alkalinizing mechanism of the duodenum.<sup>8</sup> A relative acid-alkali imbalance<sup>4</sup> and a relative deficiency of neutralizing and diluting fluid, as well as a disturbance in the neutralizing and diluting mechanism,<sup>3c</sup> have been demonstrated in patients with duodenal ulcer. There is some evidence, moreover, that the neutralizing juices, the pancreatic and the biliary in particular, are defective in such patients.<sup>16</sup>

It is difficult to conceive of immediate effective neutralization of gastric chyme as it enters the duodenum unless there is a considerable concentration of duodenal contents in the bulb. One of us (Thomas<sup>17</sup>) previously suggested that an interference with "receptive relaxation" in

13. Orndorff, J. R.; Bergh, G. S., and Ivy, A. C.: Peptic Ulcer and the "Anxiety Complex," *Surg., Gynec. & Obst.* **61**:162, 1935. Schmidt, C. R., and Fogelson, S. J.: The Effect of Physiologic Hypersecretion on the Gastro-Duodenal Mucosa, *Am. J. Physiol.* **120**:87, 1937.

14. Berk, J. E.; Thomas, J. E., and Relifuss, M. E.: The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs, *Am. J. Digest. Dis.* **9**:297, 1942.

15. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, *Am. J. Digest. Dis.* **8**:366, 1941.

16. Ask-Upmark, E.: Further Observations on the Pathogenesis of Peptic Ulcer, *Acta med. Scandinav.* **103**:280, 1940. Ivy, A. C.; Schrager, U. G., and Morgan, J. E.: Spontaneous Ulcers in Dogs with Chronic Mild Icterus, *Proc. Soc. Exper. Biol. & Med.* **30**:698, 1933. Jergesen, F. H., and Simonds, J. P.: The Blood Lipase in Patients with Peptic Ulcer, *J. Lab. & Clin. Med.* **19**:1054, 1934. McClure, C. W., and Huntzinger, M. E.: Pathologic-Physiologic Studies on Changes in the External Secretions of the Pancreas and Liver, *New England J. Med.* **206**:507, 1932. Reymont, A.: A Study of Liver Function in Experimental "Peptic" Ulcer, *Am. J. Digest. Dis.* **7**:65, 1940.

17. Thomas, J. E.: The Maximal Acidity of the Intestinal Contents During Digestion, *Am. J. Digest. Dis.* **7**:195, 1940.

the duodenum of patients with ulcer, either as a result of changes in the duodenum before the appearance of ulceration or as a result of the ulcer itself, might act to prevent an accumulation of duodenal contents in the juxtapyloric region. The retention of this neurophysiologic mechanism in normal persons and its disruption in patients with ulcer might help explain the more efficient duodenal neutralization in the former. Morton<sup>4</sup> earlier was led to believe from his experimental work that a basic defect in patients with ulcer is some derangement in the function of the pylorus which results in improper mixing of the gastric and the duodenal contents.

Attention was called to the relative independence of the graphic curves of titratable gastric acidity and of gastric  $p_H$  and to the lack of close parallelism between the several indexes of gastric acidity and the  $p_H$  in the duodenal cap. It seems justifiable to conclude that none of the customary measures of gastric acidity can be relied on with any certainty to indicate the behavior of the effective acidity ( $p_H$ ) present over the same period of time in the duodenal bulb.

#### SUMMARY AND CONCLUSIONS

1. The contents of the duodenal bulb, which is the parent site of most clinical ulcers, are more acid in patients with duodenal ulcer than in normal subjects. In patients with ulcer after an Ewald meal the contents of the duodenal bulb have an average  $p_H$  of about 3.9.

2. The ability of the contents of the first part of the duodenum to neutralize, buffer and dilute the gastric chyme is in evidence in patients with duodenal ulcer although impaired. In contrast to that of normal persons, however, the neutralizing ability of the duodenal bulb contents is overcome more frequently, to a greater extent and for longer periods of time.

3. Free acid is more frequently encountered in the contents of the first part of the duodenum in patients with an ulcer in that location than it is in normal subjects.

4. Patients with duodenal ulcer appear to differ from normal persons not only in the direction of gastric hyperacidity but in the direction of a defectiveness of the neutralizing capacity in the duodenal bulb.

5. Acid gastric juice per se is not so important a factor in duodenal ulcer as it has hitherto been considered.

6. The degree of acidity of the stomach contents is by no means the sole determinant of the degree of acidity of the duodenal bulb contents. There is no parallel relationship between the effective acidity ( $p_H$ ) in the duodenal bulb and any of the customary indexes of gastric acidity.

Dr. B. B. Vincent Lyon permitted study of the patients and use of the facilities of the gastrointestinal disease clinic, and Dr. Melvin Dillman and Dr. Karl Kornblum cooperated in performing the roentgenologic studies on each subject.

# MERCURIAL AND XANTHINE DIURETICS IN CHRONIC CONGESTIVE HEART FAILURE

A COMPARATIVE SURVEY

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The present study was made possible by employing directly the daily weight of patients with cardiac disease—the simplest and yet most accurate means of following diuretic response, great or small. A number of the commonly used diuretics were administered to these patients, including some of the more recently popularized agents which contain the combination of a xanthine derivative with a mercurial.

Before going into further details we would stress two points which seem to us of importance in consideration of previous studies on diuretics. First, most of the observations up to the present have necessarily been of relatively short duration (usually a matter of weeks) because of the time limitations placed on the hospitalization of all types of patients. Marvin,<sup>1</sup> in his studies on xanthine derivatives, emphasized the fact that his patients were under observation from only three weeks to a little over six weeks. The patients in our series were under continuous observation for an average of over forty-two weeks, because of favorable circumstances of hospitalization. Second, the evaluation of diuretic action has usually been derived from observations made on patients with far advanced congestive heart failure. It is logical to presume that in the presence of a great excess of edema fluid any one of many diuretics might conceivably produce a satisfactory response. This response, however, has been shown to vary in relation to known factors, such as digitalization and excess or deficiency of chloride ions or sodium ions.<sup>2</sup> It is our opinion that until these factors become

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1. Marvin, H. M.: The Value of the Xanthine Diuretics in Congestive Heart Failure, *J. A. M. A.* **87**:2043 (Sept. 25) 1926.

2. (a) Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J. Clin. Investigation* **3**:149, 1926.  
(b) Blumgart, H. L.; Gilligan, D.; Levy, R. C., and Brown, M. G.: The Effects

*(Footnote continued on next page)*

stabilized, any accurate survey of diuretic action must be open to question.

The present work has been restricted to the use of diuretics in 16 patients who were followed during a period which ranged from three weeks to one hundred and twelve weeks. Initially, of course, each patient had been in a state of advanced congestive heart failure. Furthermore, the condition of each patient was first controlled by the use of digitalis, ammonium salts and mercurial diuretics until all gross evidence of clinical edema was either entirely absent or minimal to the extent that the administration of a diuretic did not produce any further conspicuous drop in the average weight level of the patient, as could be seen on the daily weight chart. This state we have conveniently designated the "state of balance" (fig. 1). Figure 1 demonstrates clearly that if a given patient has received a series of injections of

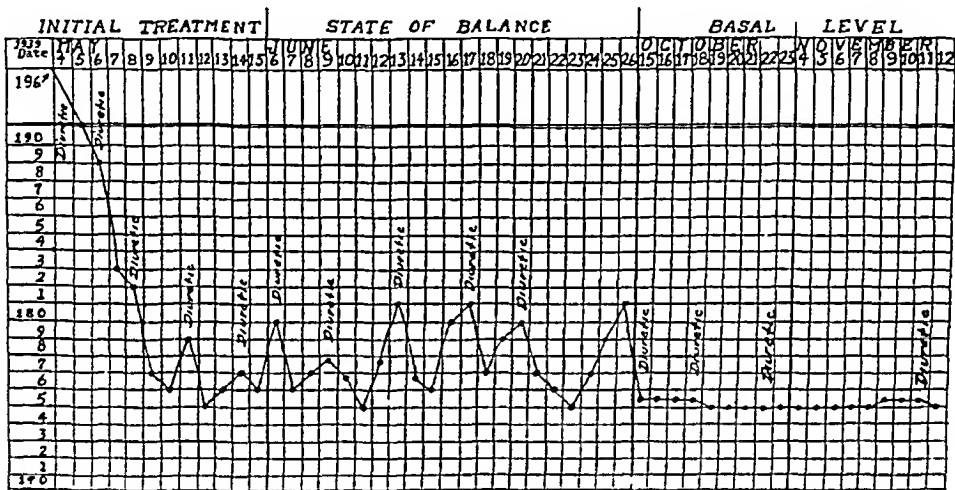


Fig. 1.—Weight chart of a patient with hydropic cardiac disease, showing achievement of a "state of balance," a condition in which the administration of a diuretic will not produce any further conspicuous drop in the average weight level.

mersalyl solution (2 cc.) at any chosen interval (e. g., four days apart) and the average resultant loss of weight recorded on the chart indicates that a uniform diuretic response is being obtained from these successive treatments, it can be considered that this patient has reached a "state of balance." This so-called "state of balance" must not be confused with the "basal level," or edema-free state, in which a diuretic is no longer capable of producing a response as indicated by the weight chart

of Diuretics on Water and Salt Metabolism, Tr. A. Am. Physicians **47**:304, 1932. (c) Ethridge, C. B.; Myers, D. W., and Fulton, M. N.: Modifying Effect of Various Inorganic Salts on Diuretic Action, Arch. Int. Med. **57**:714 (April) 1936. (d) Herrmann, G., and Decherd, G. M., Jr.: Further Studies on the Mechanism of Diuresis with Especial Reference to the Action of Some of the Newer Diuretics, J. Lab. & Clin. Med. **22**:767, 1937.

(see right side of figure 1). This point will be taken up more fully in a future publication.

We hoped that for a given agent the average of any three or four successive diuretic effects obtained during such a "state of balance" could be considered to be a more or less typical response for that drug at the selected dose. A different diuretic or a different dose of the first diuretic could then be given at the same interval, so that the two responses could be compared directly. In this way the average loss in weight could be assumed to be an accurate index of the diuretic comparability of any two drugs in a given patient. In order to be sure that the patient continued to respond to the same degree as before, a period of observation with the original drug at its first dose followed the trial of the second diuretic or the second dose, so that once again a direct comparison was obtained.

The diuretic effects which were noted in these patients before the establishment of this control period, i. e., "state of balance," have been omitted from this survey because the value of these observations was mitigated by some of the objections just mentioned. Hence, of a total of six hundred and ninety-three separate injections of the various diuretics which were administered to these 16 patients, the results from but two hundred and seventy-eight injections were considered sufficient to serve as an accurate index of the diuretic response.

In checking the literature it was noted that in some of the experimental studies on the effect of diuretics on animals a pattern somewhat similar to that adopted here was followed.<sup>3</sup> For instance, Bliss and Morrison<sup>4</sup> stated: "It should be understood that the drugs were not administered until long observation had established that the rabbits were in good balance as determined by intake, output and weight."

At the inception of this study mersalyl solution (2 cc.) was routinely employed in all cases. Occasionally, in cases in which the edema was refractory, a trial of mersalyl solution in a larger dose (4 cc.) was dared in hopes of a better response. However, anxiety over the possible toxic effects prompted the acceptance of the suggestion of Swigert and Fitz<sup>5</sup> that a smoother diuresis can be obtained when a mercurial diuretic is given in smaller and more frequent doses. Accordingly, in some cases

3. (a) DeGraff, A. C.; Batterman, R. C., and Lehman, R. A.: Influence of Theophylline upon Absorption of Mercupurin (Novurit) and Salyrgan (Mercury Preparations) from Site of Intramuscular Injection, *J. Pharmacol. & Exper. Therap.* **62**:26, 1938. (b) DeGraff, A. C.; Batterman, R. C.; Lehman, R. A., and Yasuna, E.: Excretion of Mercury Following Administration of Mercurial Diuretics With and Without Theophylline, *Proc. Soc. Exper. Biol. & Med.* **39**: 250, 1938. (c) Ethridge, Myers and Fulton.<sup>2c</sup>

4. Bliss, A. R., and Morrison, R. W.: A Comparative Study of Certain Xanthine Diuretics, *J. Tennessee M. A.* **25**:387, 1932.

5. Swigert, V. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on Plasma Volume, *J. A. M. A.* **115**:1786 (Nov. 23) 1940.

mersalyl solution was injected in doses of 1 cc. and even in doses as low as 0.5 cc. In many instances we administered some of the newer diuretics, such as mersalyl-theophylline solution (2 cc.), by injection and also orally and rectally. Finally, mersalyl solution combined with theophylline with ethylenediamine ( $7\frac{1}{2}$  grains [0.5 Gm.]) and theophylline with ethylenediamine alone ( $7\frac{1}{2}$  grains) were employed.

### RESULTS

In the construction of figure 2 the average loss of weight from the use of a given diuretic was compared in each patient with the average loss of weight following each of the other diuretics. The comparative effect of each diuretic which is represented on the chart does not indicate the actual total average diuresis (loss of weight) but demonstrates the relative efficiency of each drug compared with the other diuretics studied. All these calculations are based on the average loss of weight. The maximum diuretic response (in pounds) is represented in each patient by 100 per cent, so that a score of 100 indicates that a given agent produced a diuretic response as high as or higher than that of each of the other drugs in every case in which it was used (fig. 2).

The maximum diuretic effect in this group was obtained by somewhat varying modes of administration. It was found that an equal diuretic effect (100 per cent) was produced, first, by administering mersalyl solution in one large dose of 4 cc. and, second, by giving a 1 cc. dose of mersalyl solution one hour after an injection of theophylline with ethylenediamine ( $7\frac{1}{2}$  grains). It may be of interest to note that the greatly enhanced diuretic effect from the latter method of administration was accidentally discovered in a patient who had been given theophylline with ethylenediamine ( $7\frac{1}{2}$  grains intravenously) during an attack of paroxysmal dyspnea. By chance he was given the routine dose of mersalyl solution (1 cc. intramuscularly) one hour later. The loss of weight noted on his chart the next day revealed an unusual degree of diuresis. During subsequent observations the same effect was confirmed in this patient and in others. In each case, as can be seen on the chart (fig. 2), this method produced the greatest degree of diuresis. As a natural sequence the same combination of drugs, viz. mersalyl solution (1 cc.) and theophylline with ethylenediamine ( $7\frac{1}{2}$  grains), was administered simultaneously in one syringe, but it did not produce as great a degree of diuresis as that resulting when the drugs were given one hour apart (fig. 2). An increased dose of mersalyl solution (2 cc.) failed to alter this result. In fact, the results obtained from the simultaneous injections (65.2 per cent) were not so great as the diuretic effect produced by mersalyl solution in 2 cc. doses alone (87.7 per cent), though they were superior to the diuresis produced by mersalyl solution in doses of 1 cc. (58 per cent).

Although the effect of mersalyl solution in high doses (4 cc.) is as great as the diuretic response obtained from mersalyl solution (1 cc.) and theophylline with ethylenediamine ( $7\frac{1}{2}$  grains) given in separate injections (100 per cent), the obvious difference in the quantity of mercury in the two doses (4:1) undoubtedly makes the frequent use of mersalyl solution in such a great dose hazardous. In fact, according to the work of Barbour<sup>6</sup> on rabbits and that of Johnstone and Keith<sup>7</sup>

100	Theophylline with ethylenediamine ( $7\frac{1}{2}$ grains) followed after one hour by mersalyl solution (40 mg. Hg) 1 cc.
100	Mersalyl solution (160 mg. Hg) 4 cc.
87.7	Mersalyl solution (80 mg. Hg) 2 cc.
65.2	Mersalyl solution (40 mg. Hg) 1 cc. administered simultaneously with theophylline with ethylenediamine ( $7\frac{1}{2}$ grains)
62.5	Mersalyl solution (80 mg. Hg.) 2 cc. administered simultaneously with theophylline with ethylenediamine ( $7\frac{1}{2}$ grains)
58.0	Mersalyl-theophylline solution (40 mg. Hg; $1\frac{1}{2}$ grains of theophylline) 2 cc.
57.7	Mersalyl solution (40 mg. Hg) 1 cc.
32.0	Mersalyl solution (20 mg. Hg) 0.5 cc.
29.9	Theophylline with ethylenediamine ( $7\frac{1}{2}$ grains)
25.1	Mersalyl solution (80 mg. Hg) with theophylline (40 mg.) given orally; also mersalyl solution (160 mg. Hg.) with theophylline (157 mg.) given rectally.

Fig. 2.—Comparison of the relative efficiency of the diuretics studied. A score of 100 per cent indicates that a given agent produced a diuretic response as high as or higher than that of each of the other drugs in every case in which it was used.

6. Barbour, H. G.: Mercuric Chloride Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, *J. A. M. A.* **64**:736 (Feb. 27) 1915.

7. Johnstone, B. I., and Keith, H. M.: Toxicity of Novasurol (Merbaphen): Its Action on the Kidney of the Rabbit, *Arch. Int. Med.* **42**:189 (Aug.) 1928. Keith, H. M., and Johnstone, B. I.: The Action of Merbaphen (Novasurol) on the Kidney of the Dog: A Combined Functional and Pathologic Study, *ibid.* **44**:438 (Sept.) 1929.



on dogs, the lethal dose of merbaphen for a man weighing 70 Kg. was theoretically calculated to be 6 cc. of a 10 per cent solution.

In order to clarify the representation of these diuretics on the chart, which is on a percentage basis, a few examples of actual average loss of weight per injection are cited. Mersalyl solution (1 cc.) injected intramuscularly one hour after the intravenous administration of theophylline with ethylenediamine ( $7\frac{1}{2}$  grains) produced an average loss of weight of 5.9 pounds (2.6 Kg.), as against a loss of 3.1 pounds (1.4 Kg.) produced by mersalyl solution (1 cc.) alone or a loss of 3.5 pounds (1.6 Kg.) produced by mersalyl solution (1 cc.) and theophylline with ethylenediamine ( $7\frac{1}{2}$  grains) given simultaneously.

It should be emphasized that the "state of balance" which has been selected for this group of patients has set up a critical test for any given diuretic. Whereas reports in the literature<sup>8</sup> indicated excellent diuretic results from oral and from rectal administration of mersalyl solution and mersalyl-theophylline solution, the results from the use of these agents in this survey can be considered negligible (25 per cent). We believe that a logical explanation for the favorable results reported may lie chiefly in the practice of evaluating diuretic results in patients with a large accumulation of edema. In our patients the use of theophylline with ethylenediamine ( $7\frac{1}{2}$  grains) intravenously almost invariably failed to produce a diuretic response of any consequence (30 per cent). This seems to indicate that in this group of patients, in whom a relatively small quantity of edema remained, theophylline with ethylenediamine had no direct diuretic action; yet in conjunction with mersalyl solution, which by itself was capable of producing a good diuresis in these very same patients, theophylline with ethylenediamine actually enhanced the diuretic effect of mersalyl solution.

It can readily be seen on the chart that mersalyl-theophylline solution (2 cc.), which at this time is the only commercially available preparation containing mersalyl, produced a decidedly inferior diuretic response in this group of patients (3.03 pounds [1.3 Kg.] per injection). In fact, although this solution was given in a 2 cc. dose, the result produced (58

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8. Fulton, M. N.: Mercurin Suppositories as a Diuretic in the Treatment of Edema, *New England J. Med.* **214**:1092, 1936. Parkinson, J., and Thomson, W. A. R.: A Mercurial (Novurit) Suppository as a Diuretic for Cardiac Edema, *Lancet* **1**:16, 1936. Brightman, I. J., and Batterman, R. C.: The Treatment of Edema by Rectal Administration of Diuretics, *J. Lab. & Clin. Med.* **25**:1038, 1940. Brightman, I. J., and Lehman, R. A.: Experimental Study of Rectal Administration of Mercurial Diuretics (in Suppositories), *ibid.* **25**:56, 1939. Blackford, L. M.: Salyrgan-Theophylline by Mouth, Case of Congestive Heart Failure, *J. M. A. Georgia* **29**:397, 1940. Claiborne, T. S., and Logue, R. B.: Use of Salyrgan-Theophylline Suppositories in Congestive Heart Failure, *ibid.* **29**:399, 1940. Flexner, J.: Mercurial Suppository as a Diuretic, *Ann. Int. Med.* **11**:1962, 1938. Ethridge, Myers and Fulton.<sup>2c</sup> Herrmann and Dechard.<sup>2d</sup>

per cent) merely equals that produced by mersalyl solution given alone in a 1 cc. dose (57.7 per cent).

For some time we have been at a loss to explain this puzzling clinical phenomenon. However, the clinical observations of Wermer and Zak (1925),<sup>9</sup> confirmed in 1926 by the experimental work of Fröhlich and Zak,<sup>10</sup> demonstrated that xanthines increased the permeability of the body tissues. In 1938 DeGraff, Batterman and Lehman<sup>3a</sup> showed conclusively that both mercupurin and mersalyl solution with theophylline are absorbed almost completely within one hour after intramuscular injection and proved that the presence of theophylline influences the absorption of these mercurial diuretics to a marked extent. The same workers with an associate<sup>3b</sup> further proved that theophylline greatly increased the rate of urinary excretion of mercury after the injection of mercurin or mersalyl solution. The amount of mercury which ordinarily is excreted within six hours was increased 30 to 40 per cent after intravenous injection and 100 to 300 per cent after intramuscular injection.

Hence, despite the fact that the effect of the mercurials may be enhanced by the more rapid absorption brought about by the use of theophylline, the final effect as shown in this survey seems to indicate that the more rapid rate of excretion of mercury which follows actually tends to shorten the period of diuresis. Thus, the action of theophylline, which at first glance may serve as a most useful adjunct in hastening the absorption of the mercurials, seems to have its beneficial action in respect to absorption more than neutralized by an action in which it hastens excretion of the mercury through the urinary tract. Yet this does not explain the superlative diuretic effect obtained when mersalyl solution (1 cc.) is given separately, viz. one hour after the injection of theophylline with ethylenediamine (7½ grains). This last question must remain unanswered for the present.

#### SUMMARY

It is proposed that accurate clinical methods for the evaluation of mercurial and xanthine diuretics in patients with hydropic cardiac disease require a preliminary period of treatment until all grossly visible edema has disappeared. This disappearance has been determined from the strict use of the daily weight of the patient, and the resultant condition has been called by us a "state of balance."

In patients in this "state of balance" only the really effective diuretics are capable of producing a further diuresis.

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9. Wermer, P., and Zak, E.: *Klinische Studien über die Wirkung von Diureticis auf Gewebe*, *Wien. klin. Wchnschr.* **38**:1177, 1925.

10. Fröhlich, A., and Zak, E.: *Ueber medikamentöse Beeinflussung der Gewebsdurchlässigkeit*, *Wien. med. Wchnschr.* **39**:493, 1926.

The following observations were made on 16 patients given a total of two hundred and seventy-eight injections:

1. Injectable preparations in which mersalyl solution was combined with theophylline or theophylline with ethylenediamine were notably less efficient than pure mersalyl solution administered in similar doses.
2. Oral and rectal modes of therapy which employed combinations of mersalyl solution and theophylline produced little diuretic effect compared with that produced by injectable preparations administered to the same patients.
3. Theophylline with ethylenediamine ( $7\frac{1}{2}$  grains) given intravenously to patients in a "state of balance" did not produce any evident diuresis by itself.
4. Finally, the greatest diuresis was produced by mersalyl solution (1 cc.) given intramuscularly one hour after intravenous administration of theophylline with ethylenediamine ( $7\frac{1}{2}$  grains). A superior degree of diuresis resulted, which was equaled only by a dose of mersalyl solution alone containing four times as much mercury, namely, 4 cc.

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# HYPERACTIVE VASODEPRESSOR CAROTID SINUS REFLEX

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It has been demonstrated in recent years that blood pressure is automatically regulated by alterations in the intra-arterial pressure. This automatic regulation is maintained by a system of pressoreceptor innervations localized in different areas of the vascular tree. The most important areas of such innervations are in the aorta and, especially, in the carotid sinus regions.

Because the carotid sinus regions have easily accessible nerve terminals and because they contain the most active pressoreceptors, these areas in man have been subjected to considerable investigation in recent years.

It was the illuminating experimental work of Hering<sup>1</sup> which first demonstrated the presence of nerve connections between the carotid sinus regions and the medullary centers. He<sup>2</sup> was also the first to demonstrate the occurrence of a drop in pressure on stimulation of the carotid sinus.

Hering found that in the adventitial coat of the pouched-out area of the internal carotid artery, at its junction with the external carotid, there are present sensory receptor end organs which terminate in characteristic menisci and emerge as spiral fibers which form the sinus nerve, bearing his name. The sinus nerve merges with the glossopharyngeal nerve, which reaches the medulla. According to Brauecker,<sup>3</sup> in some animals afferent tracts from the carotid sinus region are found also in the vagus, the cervical sympathetic and the hypoglossal nerves, and the end organs of such tracts are not confined strictly to the carotid sinus but are found also in the adjacent portion of the common and the external carotid artery.

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From the Cardiologic Service, Department of Medicine, Coney Island Hospital and Harbor Hospital.

1. Hering, H. E.: *Der Karotisdruckversuch*, München. *med. Wchnschr.* **70**: 1287, 1923.

2. Hering, H. E.: *Die Karotissinusreflexe auf Herz und Gefässe*, Dresden, Theodor Steinkopff, 1927.

3. Brauecker, W.: *Das pressorezeptorische Nervensystem und seine praktische Bedeutung in der Chirurgie*, Beitr. z. klin. Chir. **158**:309, 1933.

In the medulla the afferent fibers make synaptic connections at the various areas, or so-called "centers," with the efferent neurons which run in the sympathetic, vagal and respiratory nerve systems and which control the vasomotor tone throughout the body, the heart rate and the respiration. There are also synaptic connections of the afferent tracts from the carotid sinus with other regions of the brain, resulting in various other manifestations. These will be left out of the present discussion.

Under normal conditions the carotid sinuses, together with the aortic depressor nerves, control the circulation by impulses set up as a result of arterial pressure changes within the vessels. A sudden spontaneous increase in pressure stimulates the receptor organs in these locations and sets up afferent impulses which enter the medullary region and result in vasodepression, cardioinhibition, some alteration in respiration, a decrease in the secretion of epinephrine, and so on, all of which result in a lowering of the blood pressure and slowing of the heart. A decrease in the intra-arterial pressure produces the opposite effects.

The sinus nerves have a natural tonus which helps maintain the blood pressure and the cardiac rate at certain levels at all times. This is shown by the fact that if both nerves are cut some rise in pressure and acceleration of the heart will result. Basing his theory on these facts, Hering<sup>4</sup> postulated the possibility that essential hypertension might be due to absence of the depressor reflex of the carotid arteries and of the aorta. Koch and Mies<sup>5</sup> and Heymans and Bouckaert<sup>6</sup> produced prolonged hypertension by bilateral denervation of the carotid sinus and section of the aortic depressor nerves. Their finding was corroborated by Nowak and Walker,<sup>7</sup> who produced hypertension which lasted about three years.

At the present writing the question as to how much of a role the absence or the diminution of the activity of the sinus and the aortic nerves plays in the pathogenesis of hypertension has not been answered. Heymans, Bouckaert and Regniers<sup>8</sup> in a complete review of the subject

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4. Hering, H. E.: Die klinische Bedeutung der Carotissinusreflexe, *Med. Klin.* **23**:155, 1927.

5. Koch, E., and Mies, H.: Chronischer arterieller Hochdruck durch Dauer-ausschaltung der Blutdruckzügler, *Krankheitsforschung* **7**:241, 1929.

6. Heymans, C., and Bouckaert, J. J.: Observations chez le chien en hypertension artérielle chronique et expérimentale, *Compt. rend. Soc. de biol.* **106**:471, 1931.

7. Nowak, B. I., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension, *New England J. Med.* **220**:269, 1939.

8. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933.

up to 1933 expressed the opinion that it plays a part in most cases. In some cases the sensitivity of the vasomotor center to such factors as carbon dioxide, increased hydrogen ion concentration (which may also act reflexly on the center) and ischemia is the cause. In others, those of the so-called "white hypertensives," to quote Volhard, some humoral substance freed from the kidney is responsible. In some cases all these factors may be at play.

More recently, since the work of Goldblatt and co-workers,<sup>9</sup> the theory of the renal origin of hypertension has assumed the greatest prominence. It is applied not merely to the "white hypertensives" of Volhard but to essential hypertension as well.

If hypertension is caused by the absence or diminution of activity of the carotid sinus reflex, hypertensive patients theoretically should show little or no drop in pressure on stimulation of the carotid sinus. This has not been found to be the case. On the contrary, Koch<sup>10</sup> in testing 50 subjects found that a drop in pressure occurs more frequently in hypertensive than in normal persons. He and Hering also observed that the drop in pressure is not always caused by slowing of the heart, which occurs at the same time, for by injection of atropine sulfate the cardio-inhibitory reflex may be abolished, while a drop in pressure will still occur on carotid sinus stimulation. This observation was also made by Weiss and Baker,<sup>11</sup> Mandelstamm and Lifschitz<sup>12</sup> and other authors.

To explain the occurrence of an accentuated vasodepressor reflex in cases in which it should actually be absent, Heymans and co-workers as well as Hering and other authors postulated the theory that in such cases the pressoreceptor terminals in the adventitia become insensitive to changes in intrasinal pressure, which results in hypertension. On the other hand, the same terminals become more sensitive to external compression because of sclerosis of the carotid arteries. For this reason, vasodepression occurs more frequently in carotid artery sclerosis associated with hypertension.

Comparatively small series of clinical cases in which the vasodepressor effect of the carotid sinus reflex has been studied are recorded in the literature. For this reason the following study of 700 cases in

9. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. N.: The Production of Persistent Hypertension in Dogs, *Am. J. Path.* **9**:942, 1933.

10. Koch, E.: Ueber den depressorischen Gefäßreflexe beim Karotisdruckversuche am Menschen, *München. med. Wchnschr.* **71**:704, 1924.

11. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in Causation of Fainting and Convulsions, *Medicine* **12**:298, 1933.

12. Mandelstamm, M., and Lifschitz, S.: Die Wirkung der Karotismusreflexe auf den Blutdruck beim Menschen, *Arch. f. inn. Med.* **22**:397, 1932.

which the test was carried out is recorded. The study includes an analysis of the frequency and the degree of occurrence of this reflex in the two sexes, at various ages and at various levels of blood pressure. A comparative study was also made of the frequency and the degree of cardioinhibition in relation to vasodepression.

#### MATERIAL AND METHOD OF STUDY

The patients studied were ambulatory office patients. Most of them presented evidence of some degree of cardiovascular disease. Many, however, were free from such disease.

The patients were divided into four groups. In group I were placed persons whose blood pressure was within the normal range, being less than 150 systolic and 90 diastolic; in group II, patients with low grade hypertension, the systolic pressure ranging between 151 and 175 and the diastolic between 91 and 105; in group III, patients with moderate hypertension, the systolic pressure being between 176 and 200 and the diastolic between 105 and 125, and in group IV, patients with marked hypertension, the systolic pressure being over 220 and the diastolic over 125.

In each case the heart rate and the blood pressure were determined just before the test was done. In many cases in which there was a pronounced spontaneous fluctuation in blood pressure, described in a previous communication,<sup>13</sup> two or three determinations were done before the test, and the lowest reading was used for comparison.

The test was performed with the patient in the sitting posture. Gradual pressure was applied first to the right carotid sinus region, and the results recorded, and then to the left carotid sinus region. If the patient exhibited marked cardioinhibition with stoppage of the heart, the stimulation was discontinued momentarily and then continued in gradual stages. I found that with this procedure, cardioinhibition if not extreme would soon subside, and the heart rate would return to normal or even accelerate. The blood pressure, however, would drop to its lowest level later, on continued carotid sinus stimulation. The object of abolishing cardioinhibition was to eliminate the factor of slowing or stoppage of the heart itself as a possible cause for the fall in pressure.

The lower of the two readings of the blood pressure, obtained on stimulation of the right or of the left carotid sinus, was used for comparison with the original reading, obtained just before the test was performed, and the percentage difference calculated.

The patients were divided into groups according to sex and again according to age. The degree of cardioinhibition was designated by plus marks as follows: 1 plus if slowing was less than 10 per cent of the original rate, 2 plus for 10 to 30 per cent slowing, 3 plus for 30 to 70 per cent slowing and 4 plus for stoppage of the heart for at least three seconds. If no slowing occurred the designation was a zero mark. The findings are shown in the accompanying tables and charts.

#### ANALYSIS OF FINDINGS

*General Observations.*—The effects of stimulation of the carotid sinus were slowing or stoppage of the heart, a drop in pressure and various cerebral and other manifestations described by previous authors, notably Weiss

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13. Sigler, L. H.: Spontaneous Nonrhythmic Variations in the Blood-Pressure Levels and in the "Silent Gap," *Am. J. M. Sc.* **177**:494, 1929.

and Baker<sup>11</sup> and Ferris, Capps and Weiss.<sup>14</sup> There was a pronounced variation in the incidence and in the degree of response of each of these components of the reflex. Some patients showed only, or mainly, a greater or less degree of cardioinhibition, others vasodepression and still others cerebral or other manifestations. There was also a decided difference in response on stimulation of the two carotid sinuses. Thus in some patients there was marked cardioinhibition with no drop in pressure or other manifestations with stimulation on one side and no cardioinhibition but a pronounced drop in pressure with stimulation on the other side, and so on.

The response varied to some extent with the position of the patient. A greater response usually occurred with the patient in the upright posture than with him in the dorsal recumbent position.

Cardioinhibition if present occurred before any other manifestations. The percentage of patients showing cardioinhibition in this series was about the same as in my series previously reported.<sup>15</sup> If a drop in blood pressure occurred, it commenced soon after stimulation started, and the maximum drop would develop in four to fifty seconds. The force and the duration of stimulation necessary to accomplish the maximum drop in pressure varied with different patients. The blood pressure returned to the original level in one-half to three minutes after stimulation was discontinued. Regniers<sup>16</sup> found the maximum duration of the drop in pressure after stimulation was stopped to be about two minutes.

In those patients who presented other manifestations of the reflex, such as dizziness, fainting, unconsciousness or the milder disturbances, such manifestations would occur at about the time when the blood pressure reached its lowest level or a little later.

Patients who presented marked cardioinhibition had, of course, a drop in pressure as a result of slowing or stoppage of the heart. In many the pressure would return to nearly the original level after cardioinhibition subsided, and on continuation of the stimulation the blood pressure would again drop. When a patient exhibited dangerous

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14. Ferris, E. B.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* **14**:377, 1935.

15. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex: I. The Frequency and the Degree of Response to Carotid Sinus Pressure Under Various Disease States, *Am. J. M. Sc.* **186**:110, 1933; II. The Response to Carotid Sinus Pressure at Various Ages and Heart Rates and Rhythms, *ibid.* **186**:118, 1933; Further Observations on the Carotid Sinus Reflex, *Ann. Int. Med.* **9**:1380, 1936; Hyperactive Cardioinhibitory Carotid Sinus Reflex: A Possible Aid in the Diagnosis of Coronary Disease, *Arch. Int. Med.* **67**:177 (Jan.) 1941.

16. Regniers, P.: Le sinus carotidien en clinique, *Rev. belge d. sc. méd.* **2**:207, 1930.



cerebral manifestations, the stimulation had to be discontinued before the lowest blood pressure was obtained.

Compressing the common carotid arteries below the bifurcation resulted in a rise in pressure in many of the normal and hypertensive subjects. This observation corroborates the findings of Gammon.<sup>17</sup>

*The Incidence and Degree of Response in the Various Blood Pressure Groups, in the Two Sexes.*—Of the 700 patients, 447 were males and 253 females. Of these, 393 males and 203 females showed a drop in blood pressure on stimulation of the carotid sinus. The balance, 54 males and 44 females, did not show any drop. Of this balance, 33 patients showed a rise in pressure. An occasional rise in pressure instead of a drop

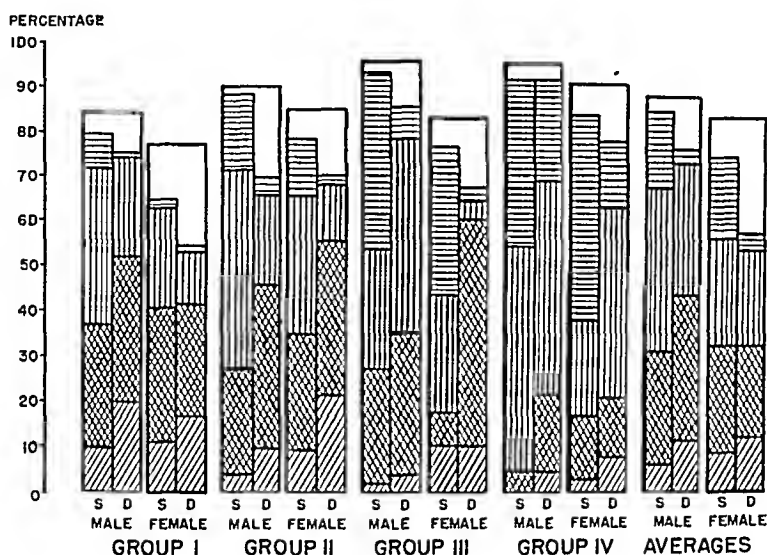


Fig. 1.—The incidence and the degree of drop in blood pressure on stimulation of the carotid sinus in 700 patients, expressed in the percentage of patients responding among males and among females in the four groups designated in table 1. Each whole bar represents the total number of patients responding. Each longitudinal semibar represents a systolic (*S*) or a diastolic (*D*) response. In the subdivisions of a semibar the degree of drop in blood pressure is represented as follows: less than 10 mm., diagonal lines; 10 to 25 mm., crosshatching; 25 to 50 mm., vertical lines, and over 50 mm., horizontal lines.

was also observed by Danielopolu and Radovici,<sup>18</sup> Marinesco and Kreindler<sup>19</sup> and other observers.

17. Gammon, G. D.: The Carotid Sinus Reflex in Patients with Hypertension, *J. Clin. Investigation* **15**:153, 1936.

18. Danielopolu, V., and Radovici, A.: Bewegungen des Unterkörpers, hervorgerufen durch der peripheren Vagusender, nach Durchschneidung des Rückenmarkes, *Klin. Wchnschr.* **6**:942, 1927.

19. Marinesco, G.; Kreindler, A., and Bruch, A.: Weitere Beiträge zum Studium der Reflexe des Sinus Caroticus in der Epilepsie, *Ztschr. f. d. ges. exper. Med.* **79**:333, 1931.

TABLE 1.—Incidence and Degree of Drop in Blood Pressure on Stimulation of the Carotid Sinus Among Males and Females Divided in Four Groups According to Blood Pressure \*

Total Number of Blood- Pressure Group		Incidence of Drop in Blood Pressure				Degree of Drop in Blood Pressure																		
						Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.						
		Male		Female		Male		Female		Male		Female		Male		Female		Male		Female				
Fe- male	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
I	242	87	203	83.9	67	77.0	192	79.3	55	63.2	21	9.9	0	10.3	26	27.3	86	35.5	19	21.8	19	7.9	1	1.1
II	122	85	111	90.0	72	84.7	109	88.5	65	76.1	1	3.2	8	9.1	22	21.5	52	42.6	26	30.5	22	18.0	9	10.5
III	60	40	57	95.0	33	82.5	56	92.2	31	77.5	1	1.6	1	10.0	3	21.6	15	25.0	10	25.0	27	15.0	14	35.0
IV	23	41	22	95.6	37	90.2	21	91.3	36	87.7	0	0.0	1	2.1	6	14.6	11	47.8	10	21.4	9	39.1	19	46.3
Total	447	253	393	87.9	209	82.6	379	82.5	187	73.9	26	5.8	22	8.7	57	25.1	161	56.6	65	25.6	77	17.2	43	17.0

\* Group I, normal blood pressure, less than 150 mm. systolic and 90 mm. diastolic; group II, low grade hypertension, pressures of 151 to 175 mm. systolic and 91 to 105 mm. diastolic; group III, moderate hypertension, pressures of 176 to 200 mm. systolic and 105 to 125 mm. diastolic, and group IV, marked hypertension, pressures over 200 mm. systolic and over 125 mm. diastolic.

Table 1 and figure 1 show the incidence and the degree of drop in pressure on stimulation of the carotid sinus in the two sexes and in each of the blood pressure groups as well as the total for all groups. Most subjects responding had a drop in both the systolic and the diastolic pressure. In some, however, there was a drop either in the systolic or in the diastolic pressure alone.

It will be noted that the incidence of response was relatively greater in males than in females. This variation was also observed by Koch.<sup>10</sup> Instead of no drop or a diminished drop in pressure, the drop was

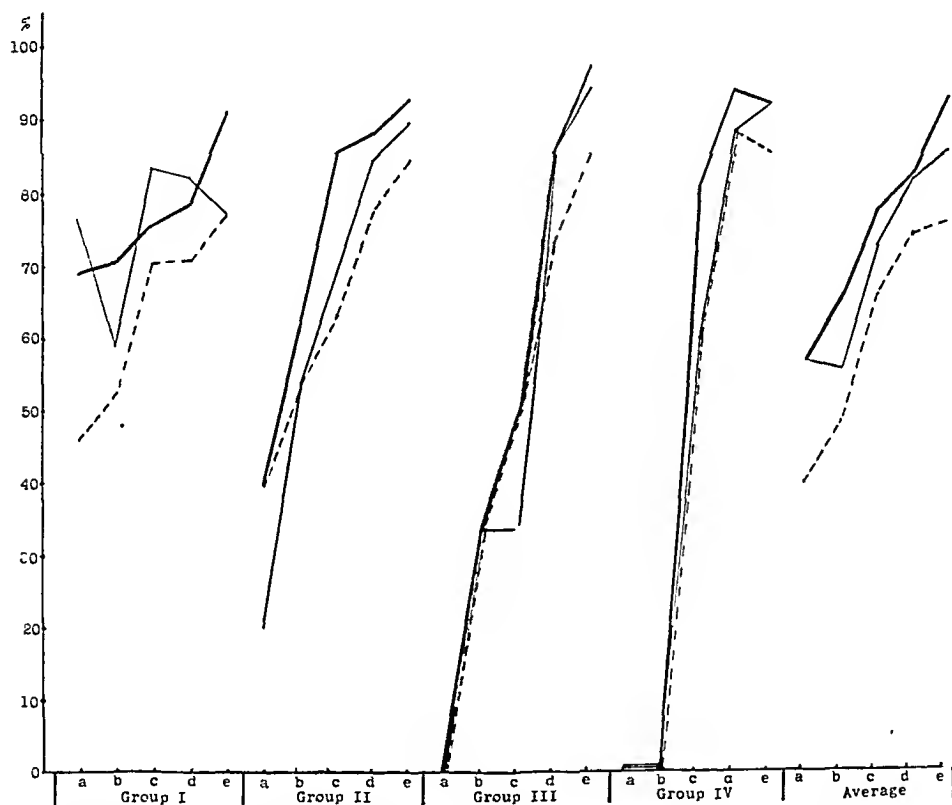


Fig. 2.—The percentage incidence of response at various ages in the four blood pressure groups designated in table 1 and the average for the four groups. The heavy solid lines represent the total number of patients that responded; the thin solid lines, the number giving a systolic response, and the broken lines, the number giving a diastolic response. In each blood pressure group ages are signified as follows: *a*, 20 years or less; *b*, 21 to 30 years; *c*, 31 to 40 years; *d*, 41 to 50 years, and *e*, over 50 years.

actually greater in hypertension. This observation corroborates the findings of Koch,<sup>10</sup> Lian, Stoicesco and Vidrasco,<sup>20</sup> Mandelstamm and

20. Lian, C.; Stoicesco, S., and Vidrasco, G.: De l'état du système nerveux végétatif dans l'hypotension et l'hypertension artérielle permanente, *Presse méd.* **37**:1309, 1929.

TABLE 2.—Incidence and Degree of Response to Stimulation of the Carotid Sinus at Various Ages in Four Blood Pressure Groups\*

Blood Pressure Group	Age of Patients, Yr.	Total Number of Patients	A. Incidence of Drop in Blood Pressure				B. Degree of Drop in Blood Pressure											
			Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
			Patients Responding		Systolic Response		Diastolic Response		Systolic		Diastolic		Systolic		Diastolic		Systolic	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	Under 20	13	9	69.2	10	76.9	6	46.1	2	15.3	4	30.6	1	39.6	2	15.3	3	23.1
	21-30	37	26	70.2	22	59.4	18	52.9	11	29.7	7	18.9	4	10.8	3	8.1	0	0.0
	31-40	64	49	75.5	47	83.9	45	70.3	5	7.8	13	20.3	25	39.0	19	29.5	16	25.0
	41-50	79	62	78.4	63	82.9	56	70.9	7	8.9	18	22.7	27	34.1	16	20.2	2	2.5
	Over 50	136	124	91.1	105	77.7	104	77.0	12	8.9	20	14.7	22	16.1	52	38.2	55	40.4
	Total	329	270	79.9	247	75.0	229	69.5	30	9.1	62	18.8	92	27.9	102	31.0	105	31.9
II	Under 20	5	2	40.0	1	20.0	2	40.0	0	0.0	1	20.0	0	0.0	0	0.0	1	20.0
	21-30	13	8	61.5	7	53.8	7	53.8	1	7.1	5	38.1	0	0.0	1	7.1	0	0.0
	31-40	30	26	86.6	25	83.3	19	63.3	0	0.0	5	16.6	15	50.0	8	26.6	9	30.0
	41-50	44	39	88.7	37	84.1	34	77.2	6	13.6	7	15.9	8	18.1	15	34.0	17	38.4
	Over 50	115	108	93.0	103	89.5	97	84.3	5	4.3	16	13.9	23	20.0	19	16.5	51	44.3
	Total	207	183	88.4	173	83.5	159	76.8	12	5.7	34	16.4	52	25.1	73	35.2	78	37.1
III	Under 20	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	21-30	3	1	33.3	1	33.3	1	33.3	0	0.0	1	33.3	0	0.0	0	0.0	1	33.3
	31-40	6	3	50.0	2	33.3	3	50.0	0	0.0	0	0.0	0	0.0	3	50.0	1	16.6
	41-50	15	13	86.6	13	86.6	11	73.3	1	6.6	0	0.0	5	33.3	7	46.6	3	20.0
	Over 50	75	73	97.3	71	94.6	64	85.3	4	5.3	5	6.6	13	17.3	14	18.6	20	26.6
	Total	100	90	90.0	87	87.0	79	79.0	5	5.0	6	6.0	18	18.0	24	24.0	25	25.0
IV	Under 20	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	21-30	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	31-40	5	4	80.0	3	60.0	3	60.0	0	0.0	0	0.0	0	0.0	0	0.0	2	40.0
	41-50	18	17	94.0	16	88.8	16	88.8	0	0.0	3	16.6	2	11.1	1	5.5	5	27.7
	Over 50	41	38	92.6	38	92.6	33	80.4	1	2.4	1	2.4	5	12.2	9	21.9	11	26.8
	Total	64	59	92.1	57	89.1	52	82.5	1	1.5	4	6.2	7	10.5	10	15.6	21	32.8
																	28	43.7
																	28	43.7
																	11	18.7

\* The blood pressure groups are the same as those designated in table 1.

Lifschitz<sup>12</sup> and others. In fact, my findings indicate that the higher the original blood pressure the greater the incidence of drop. A drop occurred more often in the systolic pressure than in the diastolic in all blood pressure groups in both males and females.

The incidence of response in this series was somewhat greater than in the series of 128 cases studied by Weiss and Baker<sup>11</sup> and the 335 cases studied by Mandelstamm and Lifschitz.<sup>12</sup> In the latter series

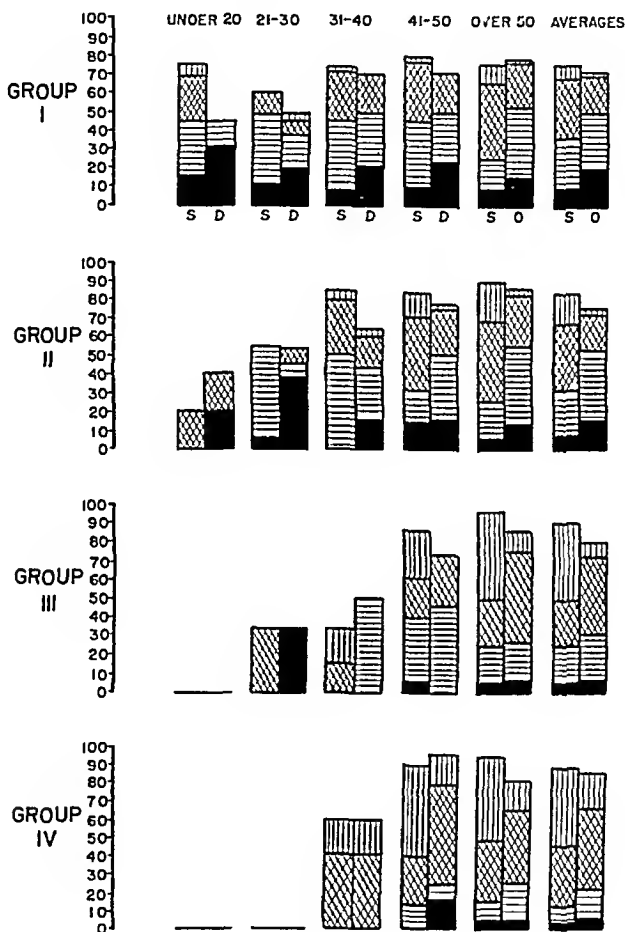


Fig. 3.—The degree of response in the various blood pressure groups at given ages, as illustrated in figure 2. Under each age group *S* stands for a systolic and *D* for a diastolic response. Representing the percentage of patients responding, the black sections signify a drop in pressure of less than 10 mm.; those with horizontal lines, a drop of 10 to 25 mm.; those with crosshatching, a drop of 25 to 50 mm., and those with vertical lines, a drop of over 50 mm.

the smaller incidence was probably due to the fact that the authors did not include among the responsive subjects those with a drop in pressure of less than 10 mm.

The degree of response, measured in millimeters of drop in pressure, also varies with the blood pressure group and with sex. Usually, the

TABLE 3.—Average Incidence and Degree of Response to Stimulation of the Carotid Sinns at Various Ages for the Entire Series of Seven Hundred Patients

Age of Patients, Yr.	Total Number of Patients	A. Incidence of Drop in Blood Pressure						B. Degree of Drop in Blood Pressure																	
		Patients Responding		Systolic Response		Diastolic Response		Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.					
								Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Under 20.....	19	11	57.9	11	57.9	8	42.1	2	10.5	5	26.3	1	5.3	2	10.5	1	5.3	1	5.3	1	5.3	0	0.0	0	0.0
21-30.....	53	35	66.0	30	56.5	26	49.0	5	9.4	13	24.3	20	37.7	8	15.1	5	9.4	1	1.9	5	9.4	0	0.0	1	1.8
31-40.....	105	82	78.1	77	73.3	70	66.6	5	4.7	18	17.1	40	38.1	30	28.4	28	26.6	20	18.9	1	0.9	4	3.8	2	1.9
41-50.....	156	131	83.9	129	82.6	117	75.0	14	8.9	38	24.3	12	7.7	15	9.6	32	20.5	41	26.3	21	13.5	4	2.6	4	2.5
Over 50.....	357	343	96.1	317	88.5	280	78.4	22	6.1	42	11.7	63	17.6	124	34.7	140	39.2	144	40.3	94	26.3	19	5.3	19	5.1

higher the original blood pressure the greater the drop. Thus, in the group with normal blood pressure and in the group with low grade hypertension a relatively greater number of patients showed a drop of less than 10 mm. than in the groups with higher grades of hypertension. In the last-mentioned groups a relatively greater number showed the higher degrees of drop in pressure. Comparatively few subjects in the normal group and in the group with low grade hypertension showed a drop of over 50 mm. In the group with the higher grades of hypertension, on the other hand, the percentage showing such a drop was great. In general, females showed a lesser degree of drop than did males in all groups.

*The Age Incidence and Degree of Response.*—In the course of this study it was found that there is a definite increase in frequency and in

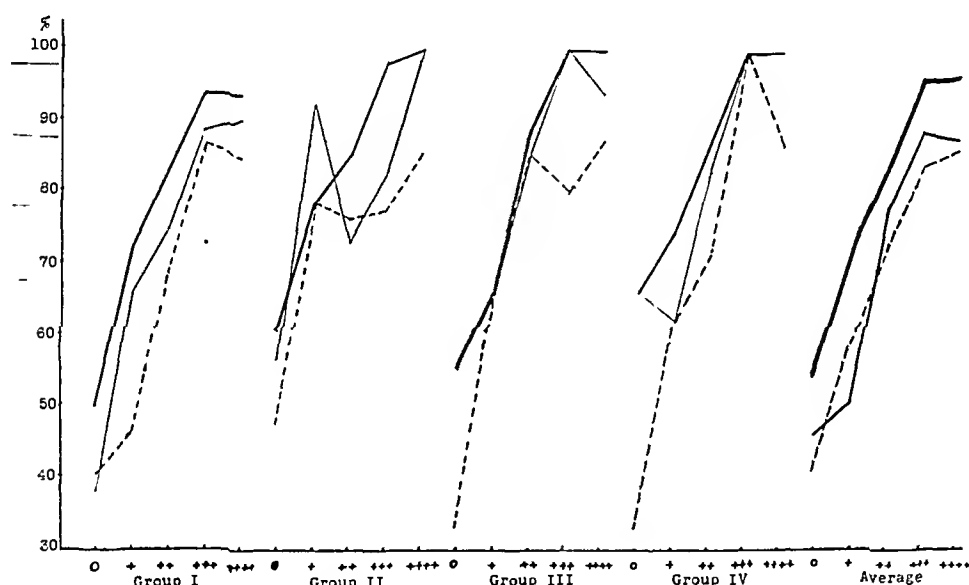


Fig. 4.—The percentage incidence of drop in blood pressure in relation to cardio-inhibition in each blood pressure group and the average for all groups. The heavy solid lines represent the number of patients that responded; the thin solid lines, the number giving a systolic response, and the broken lines, the number giving a diastolic response. The pulse marks have the same significance as those employed in table 4. The blood pressure groups are the same as those designated in table 1.

degree of response as age advances. I found no reference to this fact in the literature.

Tables 2 *A* and 3 *A* and figure 2 show the incidence of response among the 700 patients according to age and blood pressure grouping and the average for all patients.

It will be seen that in each blood pressure group the percentage of patients responding was lower at the younger ages and increased as age advanced. This observation applies both to the patients who showed

TABLE 4.—Incidence and Degree of Drop in Blood Pressure in Relation to Degree of Cardiac Inhibition in Four Blood Pressure Groups \*

Blood Pressure Group	Vagal Re- sponse †	Total Number of Patients	A. Incidence of Drop in Blood Pressure						B. Degree of Drop in Blood Pressure																		
			Patients Responding			Systolic Response			Diastolic Response			Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
																											No.
I	{ 0 + ++ +++ ++++	{ 42 49 87 61 90	{ 22 35 71 57 85	{ 50.0 71.6 82.7 93.4 93.3	{ 16 31 65 54 81	{ 38.0 63.3 74.7 88.5 90.0	{ 17 23 60 53 76	{ 40.4 46.9 68.0 86.8 84.4	{ 3 8 9 5 5	{ 7.1 16.5 10.3 8.1 5.5	{ 7 12 18 12 13	{ 16.6 24.4 26.6 19.6 13.3	{ 10 13 29 23 20	{ 23.8 26.5 33.1 32.7 22.2	{ 9 9 30 20 31	{ 21.4 18.3 31.4 32.7 36.6	{ 3 9 22 23 48	{ 7.1 18.3 25.1 37.7 53.3	{ 1 2 12 18 31	{ 2.3 40.8 13.8 28.2 36.6	{ 0 1 2 6 11	{ 0.0 20.4 2.3 9.8 12.2	{ 0 0 1 1 0	{ 0.0 0.0 1.1 1.6 0.0			
II	{ 0 + ++ +++ ++++	{ 23 28 55 59 42	{ 14 22 47 58 42	{ 60.9 78.5 85.4 93.3 100.0	{ 13 26 43 49 42	{ 56.5 92.8 78.1 83.0 100.0	{ 11 22 42 46 38	{ 47.8 78.5 76.3 77.9 90.4	{ 4 2 2 4 2	{ 17.4 0.0 3.6 6.7 4.8	{ 5 9 10 9 1	{ 21.7 32.2 18.2 15.1 2.4	{ 8 11 15 12 6	{ 31.8 39.2 27.1 20.3 14.2	{ 5 11 20 21 16	{ 21.7 39.2 26.3 35.6 38.1	{ 1 12 22 20 21	{ 4.3 42.8 40.0 33.9 50.0	{ 1 2 12 16 16	{ 1 2 7 11 13	{ 4.3 7.1 21.8 27.1 38.1	{ 0 3 4 11 13	{ 0.0 10.7 7.3 18.6 30.9	{ 0 0 0 0 5	{ 0.0 0.0 0.0 0.0 11.9		
III	{ 0 + ++ +++ ++++	{ 9 9 28 21 33	{ 5 6 25 21 33	{ 55.5 66.6 89.3 100.0 100.0	{ 5 6 24 21 31	{ 55.5 66.6 85.7 100.0 93.9	{ 3 6 24 17 29	{ 33.3 66.6 85.7 80.9 87.8	{ 1 1 2 1 0	{ 11.1 11.1 4.7 4.7 0.0	{ 1 1 4 0 0	{ 11.1 11.1 14.3 0.0 0.0	{ 2 0 5 4 7	{ 22.2 0.0 17.1 19.0 21.2	{ 1 0 9 5 9	{ 11.1 0.0 32.1 23.8 27.2	{ 0 6 8 11 11	{ 0.0 0.0 21.1 38.1 33.3	{ 0 5 10 11 15	{ 0.0 55.5 35.7 52.3 45.4	{ 2 5 10 7 15	{ 22.2 55.5 35.7 33.3 42.3	{ 0 0 0 4 4	{ 0.0 0.0 0.0 19.0 12.1			
IV	{ 0 + ++ +++ ++++	{ 3 8 18 20 15	{ 2 6 16 20 15	{ 66.6 75.0 88.8 100.0 100.0	{ 2 5 15 20 15	{ 66.6 62.5 83.3 100.0 100.0	{ 1 5 13 20 13	{ 33.3 62.5 72.2 100.0 86.6	{ 0 0 0 0 1	{ 0.0 0.0 0.0 0.0 6.6	{ 0 1 1 1 1	{ 0.0 12.5 5.5 5.0 6.6	{ 0 1 2 3 1	{ 0.0 12.5 11.1 15.0 6.6	{ 0 0 7 1 2	{ 0.0 0.0 38.8 5.0 13.3	{ 1 2 8 8 2	{ 33.3 25.0 44.4 40.0 13.3	{ 1 3 3 14 6	{ 33.3 37.5 16.6 70.0 40.0	{ 1 2 5 9 11	{ 0.0 12.5 27.7 45.0 73.3	{ 0 1 2 4 4	{ 0.0 12.5 11.1 20.0 26.6			

\* The blood pressure groups are the same as those designated in table 1.

† The degrees of cardiac inhibition are represented by the following symbols: 0, no slowing of the heart; +, less than 10 per cent slowing; ++, 10 to 30 per cent slowing; +++, 30 to 70 per cent slowing, and +++++, stoppage of the heart for three seconds or more.



a combined systolic and diastolic drop and to those who showed a drop of either the systolic or the diastolic pressure alone. The higher the original blood pressure the greater the incidence of the drop in all age groups but particularly in the older groups.

The degree of response likewise increased with advancing age, as shown in tables 2 *B* and 3 *B* and figure 3. It varied with the extent of the original blood pressure, however. In the group with normal

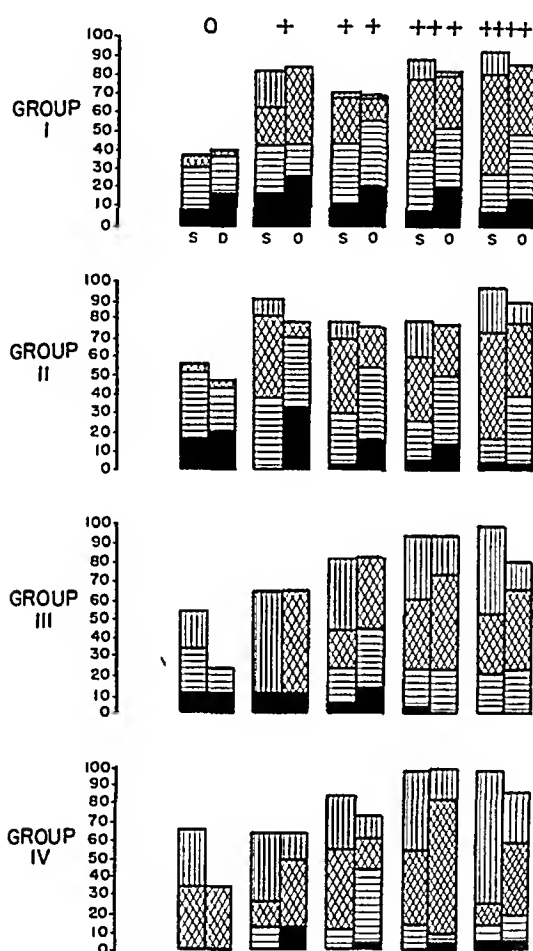


Fig. 5.—The degree of cardioinhibition in relation to the degree of fall in blood pressure. The plus marks have the same significance as those employed in table 4. The blood pressure groups are the same as those designated in table 1. The sectional subdivisions representing the degrees of drop in blood pressure are the same as those employed in figure 3; *S* signifies systolic blood pressure, and *D* signifies diastolic blood pressure.

blood pressure a relatively greater number of patients showed a low degree of drop in pressure at all ages. As the blood pressure rose, the degree of drop increased in every age group, but the increase was always greater at the older ages.

TABLE 5.—Incidence and Degree of Drop in Blood Pressure in Relation to Degree of Cardiac Inhibition for the Entire Series of Seven Hundred Patients

Vagal Response *	Total Number of Patients	A. Incidence of Drop in Blood Pressure						B. Degree of Drop in Blood Pressure															
		Patients Responding		Systolic Response		Diastolic Response		Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
								Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	.....	43	55.8	36	46.7	32	41.5	8	10.3	13	16.8	20	25.9	15	19.1	5	6.4	3	3.8	3	3.8	0	0.0
+	.....	69	73.4	68	51.0	56	59.5	9	9.5	23	24.1	25	26.4	20	21.2	23	24.4	12	12.7	11	11.6	1	1.1
++	.....	159	84.0	147	78.2	139	73.9	13	6.9	33	17.5	51	27.1	66	35.1	58	30.8	37	19.6	21	11.1	3	1.5
+++	.....	156	96.8	144	89.4	136	84.4	10	6.2	22	13.0	39	24.2	47	29.1	59	36.6	59	36.6	33	20.4	9	5.6
++++	.....	175	97.2	169	88.3	156	86.6	8	4.4	15	8.3	34	13.3	61	33.8	84	46.6	68	37.7	48	26.6	13	7.2

\* See table 4 for the designation of degrees of cardiac inhibition.

*The Relation of the Vasodepressor to the Cardioinhibitory Reflex.*—

As said before, the vasodepressor and the cardioinhibitory reflex may coexist in the same or in different degrees in the same person; both may be absent, or each may occur alone. The incidence of their coexistence and the degree of the two reflexes are shown in tables 4 A, 4 B, 5 A and 5 B and in figures 4 and 5.

It will be noted that a good proportion of patients who showed no cardioinhibition had the vasodepressor reflex. The degree of drop in pressure in such patients was on the average relatively smaller than in those who also showed cardioinhibition. Also, a fairly large proportion of patients who showed no vasodepression showed cardioinhibition. In these persons, however, the very high degree of cardioinhibition were not observed except in the group with normal blood pressure.

In general, the greatest number of patients showing cardioinhibition also showed vasodepression, and the degrees of the two reflexes on the whole corresponded.

COMMENT

It is not my intention in this paper to prove or disprove Hering's theory that hypertension may be caused by absence of the vasodepressor reflex of the aortic nerves and the carotid sinuses. Mannaberg's<sup>21</sup> contention that he found no slowing of the heart in his series of 241 hypertensive patients, which is offered as proof that the carotid sinus sensory receptors are insensitive to endarterial pressure, cannot be definitely substantiated. In my series the average heart rate was about the same in the normal as in the hypertensive subjects. Also, the finding by Hering and others that diminution in the endosinal pressure due to compression of the common carotid arteries failed to raise the blood pressure in hypertensive patients, as it would be expected to do if the carotid sinus nerve terminals had normal function, could not be substantiated in Gammon's<sup>17</sup> cases and in some of the cases in which I tried it.

Regardless of whether or not insensitivity of the sinus regions and the aortic depressor nerves is the cause or one of the causes of essential hypertension, and especially if it is the cause, the mechanism of a hyperactive vasodepressor carotid sinus reflex has not as yet been explained. Why a hyperactive reflex occurs with great frequency and in a higher degree in hypertension and why its frequency and degree increase with an increase in blood pressure still call for an explanation, as do its increase with advancing age and its more frequent occurrence in males.

That the hyperactive reflex is caused by an increase in local sensitivity of the nerve terminals because of degenerative changes in the carotid

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21. Mannaberg, J., cited by Heymans, Bouckaert and Regniers.<sup>8</sup>

arteries is not conceivable. Also, that compression of the nerve terminals against a rigid calcified sclerotic intima, as suggested by Sunder-Plassmann,<sup>22</sup> may be the cause is possible only in a few cases, in which there is local calcification of the carotid artery. In the great majority of cases there are not enough local arterial changes which would provide greater resistance to compression of the nerve terminals than that offered by the spinal column, against which the carotid sinus is compressed in performance of the test. Furthermore, many patients with pronounced local sclerosis show no hyperactivity. The lack of a relationship between a hyperactive reflex and local sclerosis of the carotid arteries was best demonstrated in the autopsy material reported on by Keele.<sup>23</sup> Finally, the fact that the response is usually greater with the patient in the upright position than with him in the recumbent posture speaks against fixed local pathologic change in the carotid arteries as the cause for hypersensitivity.

In the light of these findings, it must be assumed that a hyperactive vasodepressor carotid sinus reflex is due to changes in the synapses between the afferent and the efferent portions of the arc in the medulla or to localized changes in the vasomotor terminals of the vessels which make them lose their tonic effect reflexly.

The unequal effect of the carotid sinus reflex on the blood pressure and pulse rate and in the production of other manifestations in the same person is most likely due to differences in the threshold of the central synapses and possibly also to differences in sensitivity of the various motor arms, as suggested by Weiss, Capps and Ferris.<sup>24</sup> The probability that variation in the number and in the sensitivity of the various nerve fibers leading from the carotid sinus to different regions in the medulla is to be considered. If, however, a response is due to sensitivity in the center rather than in the carotid sinus region, such an alternative cannot be definitely considered. The experimental work of Hatcher and Weiss<sup>25</sup> is of interest in pointing to this conception. They found that a drug applied to the same area of the medulla may produce various motor effects depending on the state of the body. Different drugs applied to the same medullary region under the same bodily conditions resulted in different responses, owing probably to a specific structural affinity of the drug for given synapses. They concluded that

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22. Sunder-Plassmann, cited by Heymans, Bouckaert and Regniers.<sup>8</sup>

23. Keele, C. A.: Pathological Changes in Carotid Sinus and Their Relation to Hypertension, *Quart. J. Med.* **2**:213, 1933.

24. Weiss, S.; Capps, R. B., and Ferris, E. B.: Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex, *Arch. Int. Med.* **58**:407 (Sept.) 1936.

25. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, *J. Pharmacol. & Exper. Therap.* **22**:139, 1923.

there is considerable variation in the function of the brain centers not only in different persons but in the same person during different bodily states.

If these hypotheses are true it may be concluded that a hyperactive vasodepressor carotid sinus reflex indicates an instability in the synapses of the medullary center or in the efferent arm of the arc, which under certain provocation results in loss of the vasodepressor effect. Persons who have this unstable state may react in the same way to reflex stimulation from any region of the body, as indicated by Ferris, Capps and Weiss.<sup>26</sup> My report in this paper suggests that the instability becomes more marked as age advances and in the pathologic state of hypertension and is more prominent in males. The possibility is that local circulatory disturbances in the medulla or in the efferent endings of the vasomotor system in the vascular tree caused by arteriosclerosis may be the underlying factor, as this instability occurs under circumstances in which arteriosclerosis is apt to be present. In some persons it may be an inherent constitutional defect.

#### SUMMARY AND CONCLUSIONS

This paper covers a study of the vasodepressor effect induced by the carotid sinus reflex. Seven hundred patients were tested, most of whom had demonstrable cardiovascular disease. Of these, 447 were males and 253 females.

The patients were divided into four groups according to the original blood pressure. In group I were included subjects with normal blood pressure; in group II, patients with low grade hypertension; in group III, those with moderate hypertension, and in group IV those with marked hypertension.

It was found that, roughly, about 88 per cent of the males and 82 per cent of the females showed a drop in pressure. If a drop of less than 10 mm. is excluded as of insufficient significance, the response is reduced to about 78 per cent for males and 71 per cent for females. The response occurred more frequently and in greater degree in the older age groups. Also, the higher the blood pressure the more frequent the response and the greater its degree. A drop was more frequent in the systolic pressure than in the diastolic. A drop in pressure often occurred in patients without cardioinhibition but was more frequent in those who also showed cardioinhibition. In such patients the frequency and the degree of vasodepression roughly corresponded to those of cardioinhibition.

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26. Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Relation of the Carotid Sinus to the Automatic Nervous System and the Neuroses, *Arch. Neurol. & Psychiat.* **37**:365 (Feb.) 1937.

There was a marked difference in response to stimulation on the two sides in many cases. The amount of stimulation required to produce the maximum response varied from case to case and with the position of the patient.

The findings point to the existence of an inherent instability in the vasomotor system in persons who show a marked vasodepression induced by the carotid sinus reflex, which the test helps to demonstrate. The seat of this instability is either in the medullary synapses or in the vasomotor terminals in the vascular tree. Arteriosclerosis is possibly one of the underlying predisposing causes of such instability, as evidenced by the fact that the reflex is most prevalent under circumstances in which arteriosclerosis is apt to occur, that is, when the patient is a man, is of advanced age and has a high degree of hypertension.

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# ROENTGEN RAY TREATMENT OF HYPERTHYROIDISM

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Hyperthyroidism holds a unique position among the diseases properly falling into the field of internal medicine because, although its causation is unknown, an empiric treatment has been evolved that is satisfactory in the majority of cases. Except in certain situations, the factors that cause the thyroid to hyperfunction are obscure. Yet in most cases subtotal ablation of the thyroid relieves most of the symptoms.

In the early years of the twentieth century, the roentgen ray frequently was employed as a means of destroying the thyroid, and evidences of its success are abundant.<sup>1</sup> Its use became extensive at that time because of the high surgical mortality. However, since 1923 the preoperative preparation of patients with administration of iodine and other measures has brought about a decline in surgical mortality.<sup>2</sup> Consequently, at the present time in the major clinics of this country the mortality rate is from

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Read at the Twenty-Seventh Annual Meeting of the Radiological Society of North America on Dec. 5, 1941.

From the Divisions of Medicine and Radiology and the Thyroid Committee of the University of California Medical School and Hospital.

The members of the Thyroid Committee are Dr. Henry H. Searls, Dr. Carl L. Hoag, Dr. H. G. Bell and Dr. Leon Goldman, of the Department of Surgery; Dr. Karl B. Eichorn, of the Department of Pathology; Dr. Robert S. Stone, of the Department of Radiology; Dr. W. J. Kerr, Dr. Evelyn Anderson and Dr. Mayo H. Soley, of the Department of Medicine, and Dr. W. A. Reilly, of the Department of Pediatrics.

1. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, *Arch. Int. Med.* **31**:303 (March) 1923. Pfahler, G. E.: Roentgen-Ray Treatment of Hyperthyroidism, *Radiology* **34**:43-52, 1940 (with comprehensive bibliography). Smith, A. D., and Stenstrom, K. W.: X-Ray Therapy in Diffuse Hyperplasia of the Thyroid, *Tr. Third Internat. Goiter Conf. & Am. A. Study of Goiter*, 1938, pp. 527-532.

2. Thompson, W. O.; Taylor, S. G., III, and Meyer, K. A.: Factors Influencing Operative Mortality in Exophthalmic Goiter, *Ann. Int. Med.* **8**:350-359, 1934. Thompson, W. O.; Taylor, S. G., III; Meyer, K. A., and McNealy, R. W.: Experiences in Treating Toxic Goiter in a Large Public Hospital, *Ann. Int. Med.* **12**:217-231, 1938.

0.5 to 2 per cent during the immediate postoperative period, although in many hospitals it still is several times the latter figure. Because of the reduction in surgical mortality, many of the foremost students in this country believe that subtotal thyroidectomy is the treatment of choice for hyperthyroidism and give little credit to roentgen ray therapy.

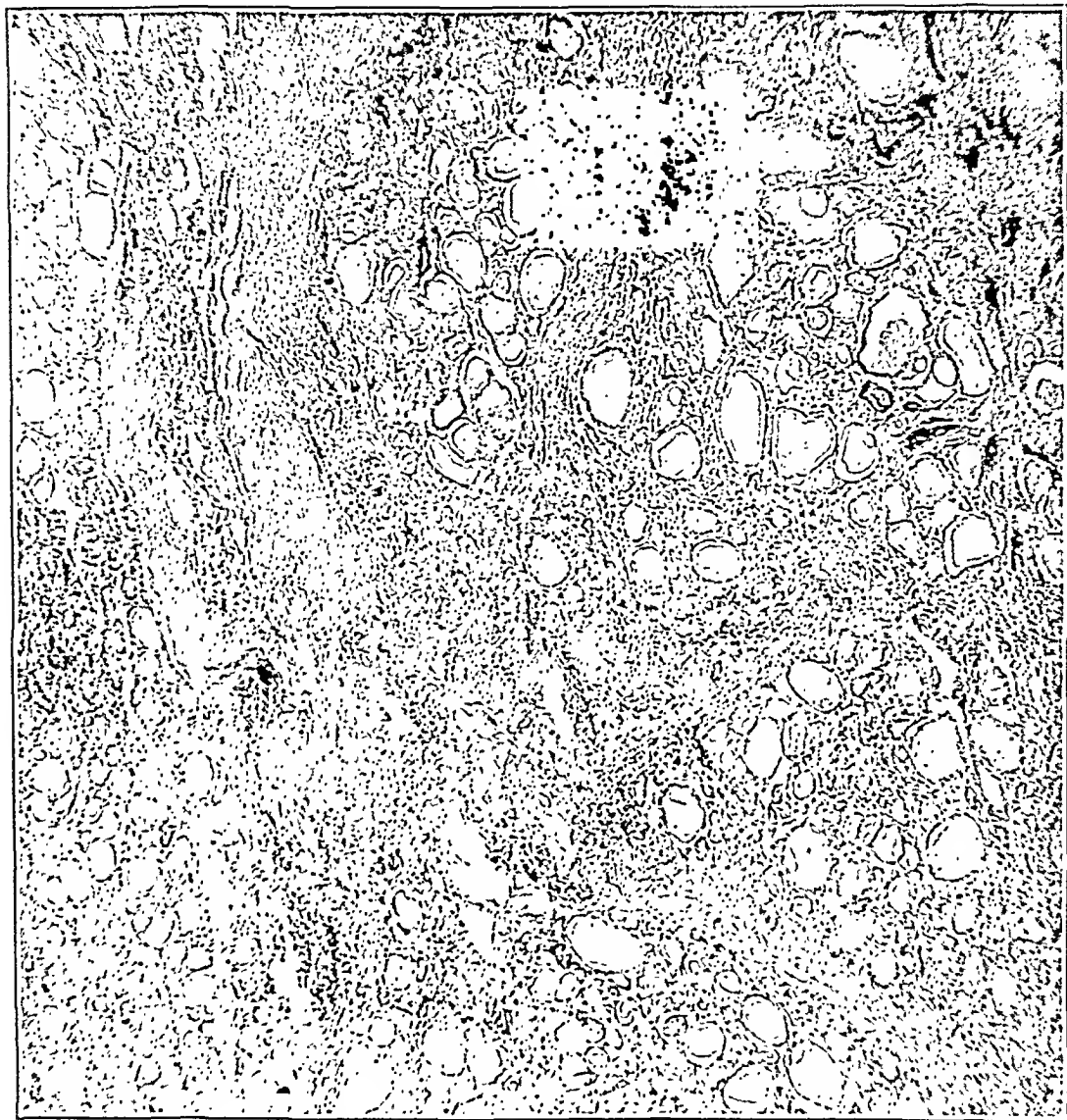


Fig. 1.—Low power section of thyroid tissue from a patient cured of exophthalmic goiter by roentgen irradiation (patient died four years after treatment of a tumor of the brain).

Roentgen rays have a profound effect not only on the smaller arterial vessels that supply the thyroid but on the acini and the supporting structures of the gland. Figures 1 and 2 show sections of thyroid tissue from a patient who had had hyperthyroidism with a metabolic rate in the low plus thirty's. After adequate roentgen ray therapy his metabolism had fallen to about — 30 per cent and his clinical symptoms had been relieved.



Four years later he died from a tumor of the brain. The thyroid tissue obtained at autopsy was firm and hard and weighed only a few grams. On microscopic examination it showed extensive fibrosis, destruction of the acini and intimal, subintimal and medial thickening of the smaller arteries. Probably the thyroids of most of the patients "cured" by roentgen ray treatment would present a similar appearance both grossly

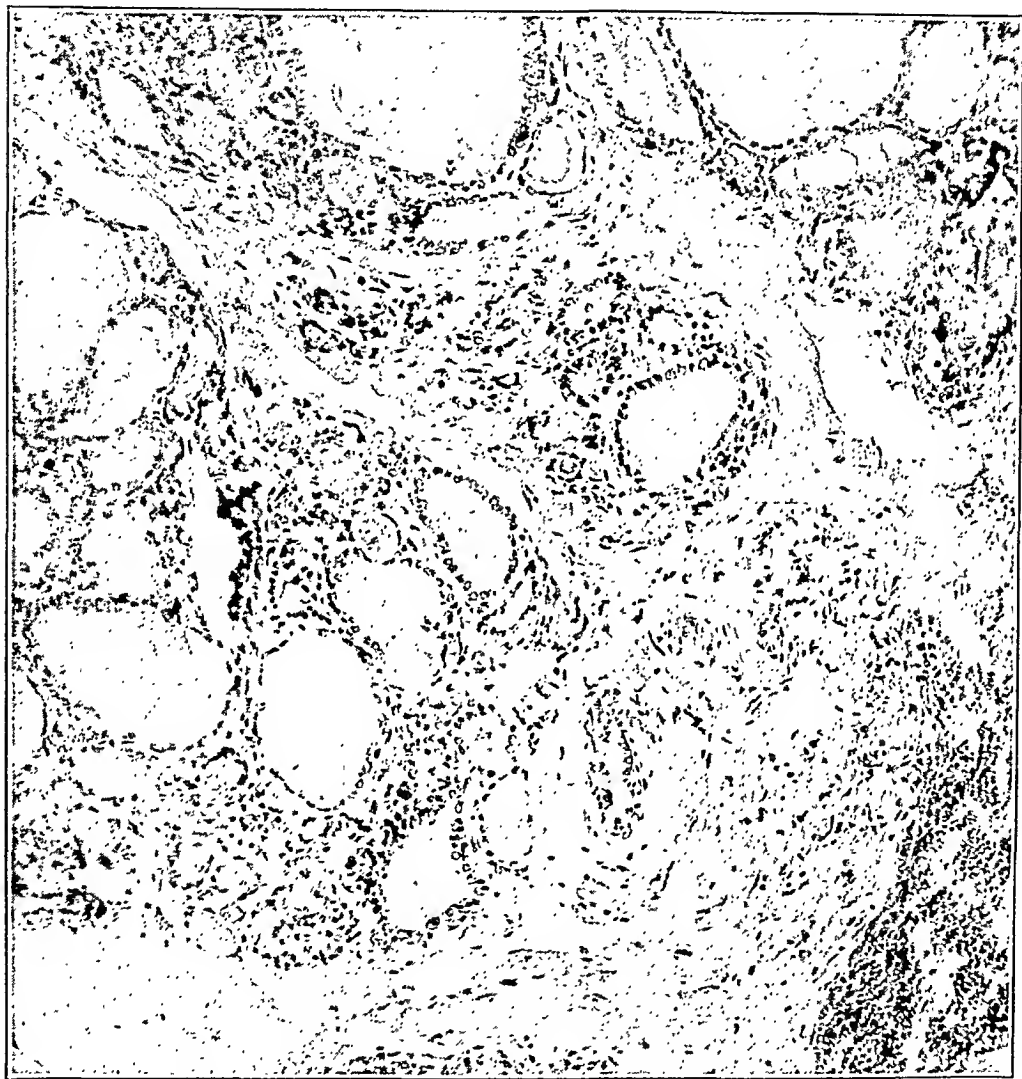


Fig. 2.—Higher magnification of tissue shown in figure 1.

and histologically. Figures 3 and 4 show sections of thyroid tissue from a young girl with extremely severe hyperthyroidism. She had been treated intensively with roentgen rays up to six weeks prior to subtotal thyroidectomy as preparation for the surgical procedure. The tissue from this patient shows an earlier stage of destruction than that from the previous patient, but again there are pronounced fibrosis, destruction of much of the acinar tissue and thickening of the smaller vessels. The

sections from these 2 patients give evidence of the ability of roentgen rays to destroy hyperplastic thyroid tissue and demonstrate the changes that might be expected as a result of successful roentgen ray therapy.

The following study was undertaken because of the neglect of roentgen ray therapy in recent years. Certain definite purposes were kept in mind: first, to determine as far as could be done by clinical examination

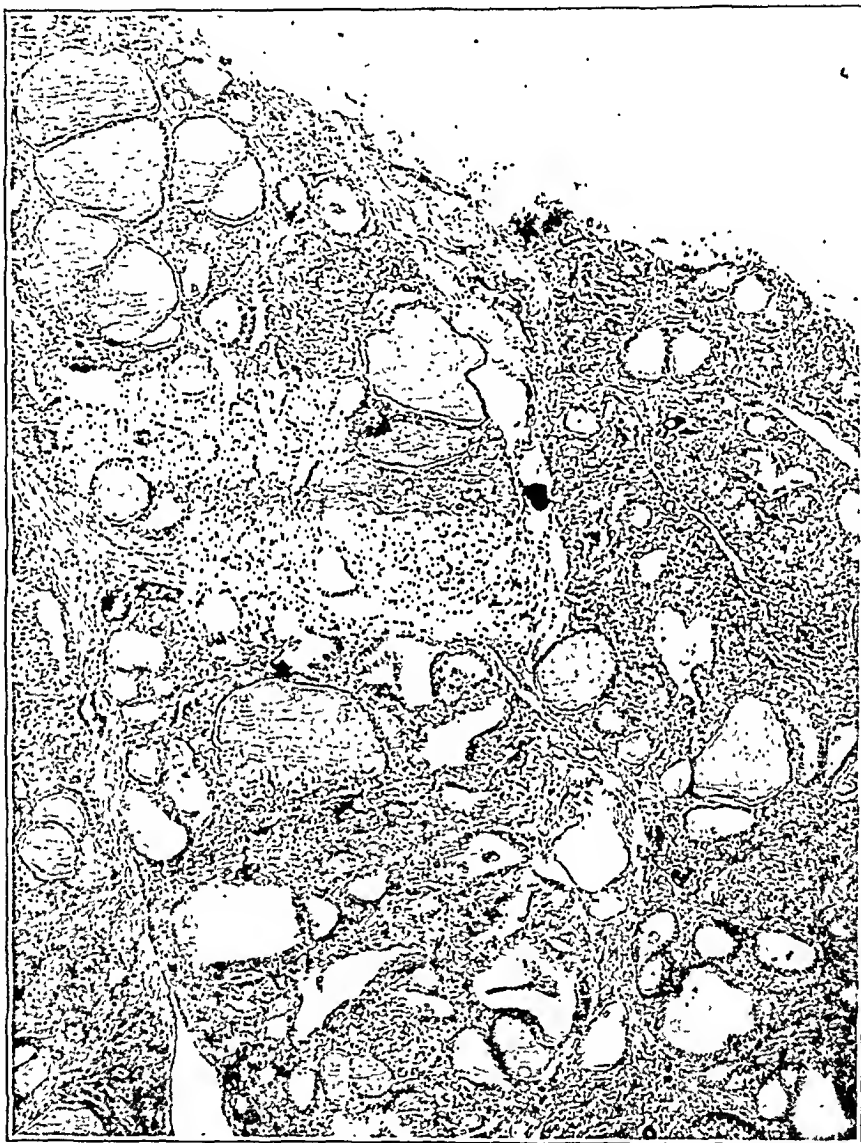


Fig. 3.—Section of thyroid tissue from a patient who received extensive irradiation to the thyroid (two courses) up to six weeks before subtotal thyroidectomy. This patient received irradiation preparatory to surgical treatment.

and laboratory tests whether or not subtotal destruction of the thyroid could be achieved and if it could be what dosage was necessary; secondly, to outline criteria for the selection of patients for whom roentgen ray therapy might be the treatment of choice, and, thirdly, to present a series

of patients who were followed carefully by one observer over a period of several years. (The method of following patients is illustrated in table 1.)

All the patients in our relatively small series of 43<sup>3</sup> had unquestioned hyperthyroidism. The selection was carried out in part by the members of the Thyroid Committee of the University of California Hospital. This



Fig. 4.—Higher magnification of tissue shown in figure 3. Note the fibrosis and change in blood vessels.

committee consists of a group of internists, surgeons, roentgenologists and pathologists particularly interested in diseases of the thyroid. It has

3. These comprised only the group seen in the clinic. A total of over 200 patients, both clinic and private, were seen by the members of the Thyroid Committee during the last twelve years; however, they were not followed in a manner that would allow an adequate and objective appraisal of the ability of roentgen rays to achieve a subtotal destruction of hyperplastic thyroids.

TABLE 1.—Record Illustrating Method of Following Patients

Name: Lena Dinnecl.		O.P. D. No.: U4395.		Age: 37 years.		Diagnosis: Toxic nodular goiter.													
Date	Therapy	Basal Metabolic		Pulse	Rhythm	Blood Pressure	Goiter	Eye Signs	Nervousness	Tremor	Dyspnea	Palpitation	Tachycardia	Weakness	Heat Intolerance	Headache	Gastro-intestinal Data	Catamenia	Comment
		Weight	Rate																
3/20/36	.....	.....	+58%	.....	120	Reg.	160/80	+	++	+	+	++	++	++	+	Occ.	++	Reg. and scanty	
3/30/36	No iodine except iodized salt	137.3	+38%	120	Reg.	160/80	+	(nodular)	++	+	+	++	++	++	+	Occ.	++		
4/21/36 to 4/27/36	Roentgen therapy																		
4/27/36	Phenobarbital 0/015, 4 i. d.	142½	.....	114	S. A.	140/71	+	+	++	+	+	++	++	++	+	Occ.	—	Flow greater	
6/ 1/36	Phenobarbital 0/015, 4 i. d.	145½	.....	102	S. A.	156/80	+	Stare only	+	Sl.	Sl.	++	+	—	+	Occ.	—	Scanty	
6/20/36	None since 6/1/36	147½	.....	72-75	S. A.	121/80	+	Stare only	—	—	—	+	±	—	Less	Less	—	Less scanty	
6/15-6/20	Roentgen therapy																		
8/ 6/36	None	149	—18%	72	Reg.	138/86	+	Stare only	—	—	—	—	—	—	—	Occ.	Reg.	Less scanty	
1/26/37	None	148½	+ 9%	81	Reg.	134/80	Less	—	—	—	—	—	—	—	—	Occ.	Const.	Sl. scanty	
3/ 1/37	None	152	.....	78	Reg.	110/80	Palpable only	—	—	—	—	—	—	—	—	Occ.	Const.	Sl. scanty	
5/10/37	None	151	0	78	Reg.	160/88	Palpable only	—	+	—	—	Occ.	—	—	—	Occ.	Const.	Sl. scanty	
4/25/38	None	152½	+15%	84	Reg.	162/100	Palpable only	—	+	—	—	+	—	—	—	—	—	Sl. scanty	
5/ 4/38	Phenobarbital 0/032 t. i. d. since 4/25/38	155½	+13%	72	Reg.	170/90	Same	—	Less	—	—	+	—	—	—	—	—	1 day shorter	
5/9/38 to 5/14/38	Roentgen therapy																		
9/23/38	None for 3 months	163½	.....	72	Reg.	132/84	Same	—	—	—	—	—	—	—	—	—	—	Reg. and normal	
12/13/38	None (diet reduced)	165	— 9%	72	Reg.	166/90	Normal size; nodular	—	—	—	—	—	—	—	—	—	—	Reg. and normal	
6/20/39	None	158½	.....	72	Reg.	134/82	Normal size; nodular	—	—	—	—	—	—	—	—	—	—	Reg. and normal	Hot flashes
1/19/40	None	167½	—16%	72	Reg.	148/90	Barely palpable; nodular	—	+	—	—	+	+	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea
9/13/40	None	167	.....	78	Reg.	134/90	Barely palpable; nodular	—	+	—	—	+	—	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea
3/11/41	None	165	.....	..	.....	.....	Barely palpable; nodular	—	Occ.	—	—	Occ.	Occ.	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea
(Patient in menopause and very worried about son who has been drafted into army)																			
8/15/41	None (Still upset about son)	162	.....	78	S. A.	170/100	Barely palpable; nodular	—	Occ.	—	—	Occ.	Occ.	—	—	—	—	Reg. and normal	

been in existence since 1929 and meets once a week to discuss problem cases and to guide the therapy of all clinic patients at the University of California Hospital. In the choice of patients for roentgen ray therapy, the following criteria were applied: 1. Only patients who were moderately ill with hyperthyroidism were chosen; patients about whom there was doubt were excluded, and very toxic patients were excluded whenever possible. 2. Patients without complications, such as rheumatic heart disease with mitral stenosis, were preferred. 3. As soon as it had been proved that patients with nodular goiter could be "cured" by treatment with roentgen rays, other such patients were omitted from this series. Thereafter only those patients were included who had had undoubted exophthalmic goiter and had a postoperative recurrence as a result of which the thyroid felt nodular on palpation but who, according to our experience with similar patients, probably did not have true or encapsulated adenoma. 4. The breadwinner of a family was not chosen for roentgen ray therapy unless the disease was of such a degree of severity that he could continue to work while undergoing treatment. 5. Patients with pulmonary tuberculosis or other diseases of the apexes of the lungs were preferably excluded. 6. For obvious reasons patients who lived at great distances were omitted from this series. Points 4 and 6 would not necessarily apply to private patients or to patients not included in a study of this kind.

#### TECHNIC

The technic of the roentgen treatment of hyperthyroidism has undergone many changes over a period of years. Since the present series of treatments was begun, only one change, namely a change in voltage, has been made. In the majority of cases the treatments were given with roentgen rays produced by a current with 100 kilovolts and 10 milliamperes of constant potential. The radiations were filtered through 0.25 mm. of copper and 1 mm. of aluminum, a beam with a half value layer of 6.8 mm. of aluminum being produced. The target-skin distance used was 40 cm., and the number of roentgens was approximately 20 per minute (measured in air). Treatments were directed to each lobe of the thyroid separately, and the fields were made large enough so that they extended beyond the limits of the lobe. They frequently were 10 by 7 or 10 by 8 cm. in size. The lower border of the thyroid fields was made to coincide with the upper edge of the sternum. A narrow strip of skin was left between the two oblique fields. The thymus field extended in the midline from the top of the sternum down 10 cm. The radiations were directed obliquely inward from each lateral field. In adjusting the angle an attempt was made not to cross fire but to direct the beam as nearly perpendicularly to the skin as possible. When the angles were such that there was cross fire at the level of the back of the trachea or the esophagus, the patient had considerable reaction, with irritation of either or both these structures.

In routine treatment the patients received 150 roentgens, as measured in air, to each lobe of the thyroid every day for six days; thus, a total of 900 roentgens (in air) was administered to each lobe. During the same period the patients

received 150 roentgens (in air) every second day to the thymus region, so that during the six day period a total of 450 roentgens was administered to the thymus. Such a series of irradiations completed what we term one course of treatment. During the following two or three weeks the patients frequently showed faint erythema or slight but persistent pigmentation. As stated, whenever a cross fire effect on the esophagus or on the trachea was created from fields that were too oblique, some irritation of the mucosa of these structures followed, which caused difficulty in swallowing or an irritative cough.

This technic was used for all patients in the series except those who received treatments on the 200 kilovolt apparatus. This apparatus consisted of a constant potential machine; the rays were filtered through 0.7 mm. of copper and 1 mm. of aluminum at a distance of 50 cm. The half value layer of this radiation was 1.05 mm. of copper. In one series to one patient and in three series to another patient, a course of treatments was given over one anterior field 10 by 10 cm. in size to the thyroid and over a field of the same size to the thymus. Since this type of irradiation is given at a greater target-skin distance and affords no chance of cross fire on the esophagus, we believe equally good results are obtained without the risk of certain adverse effects. Although the stated dose, 150 roentgens in air, is not the same on the skin when it is delivered by the different qualities of radiation (100 kilovolts and 200 kilovolts) because of difference in back scatter, the dose delivered to the tissue of the thyroid gland is so nearly the same that we consider the two methods equally satisfactory.

After a one week course of radiation, the patient was kept under medical observation for six weeks, during the last week of which time he was reexamined. Unless he showed remarkable improvement (as did 1 patient), he was given a second course of treatments, which was administered in the same manner. Again, a period of observation of about twelve weeks followed, during the last week of which the patient's condition was thoroughly reevaluated and a decision was reached as to whether or not a third course should be given. We believe definitely that treatment should not be discontinued until the clinical findings, including the basal metabolic rate, are normal or below normal. The cause for most of the recurrences which follow roentgen ray treatment is the failure to accomplish subtotal destruction of the thyroid.

Before the present method was adopted, treatments were given once a week and to only one lobe of the thyroid at a time. Later treatment was given once a week to both lobes of the thyroid and to the thymus. By the present technic, the necessary amount of radiation is administered in a comparatively short period of time with only a slight cutaneous reaction, and a period of comparative freedom from symptoms intervenes before further therapy becomes necessary.

## RESULTS

The present study was begun in 1935. From that time until September 1940, 43 patients with unquestioned hyperthyroidism were treated with roentgen rays in the clinic service of the University of California Hospital. Of these, 31 patients had toxic diffuse goiter and 12 had toxic nodular goiter. Of the 12 patients with nodular goiter, 7 gave a history of previous operation for exophthalmic goiter and had recurrences of nodular goiter clinically, 2 had long-standing hyperthyroidism and what might be called nodular involution and 3 had toxic

nodular goiter not previously treated. Thirty patients of the series had not been treated surgically, and 13 had recurrences after operation. The basal metabolic rate was determined prior to treatment for all patients except 1 who had pneumonia. The average metabolic rate was + 35.7 per cent before treatment and — 2 per cent after treatment. The average fall in basal metabolic rate was 35.7 per cent for the 37 patients who were either “cured” or showed marked improvement. Table 2 gives the pertinent data.

TABLE 2.—*Data on Forty-Three Patients with Hyperthyroidism*

Total number of patients.....	43
Women (average age 40.0 years).....	37
Men (average age 46.7 years).....	6
Classification	
Toxic diffuse goiter.....	31
Toxic nodular goiter.....	12
Recurrence of nodular goiter.....	7
Nodular involution .....	2
Toxic nodular goiter.....	3
Number of patients not previously operated on.....	30
Number of patients previously operated on.....	13
Number of patients who received iodine.....	22
Number of patients who did not receive iodine.....	21

TABLE 3.—*Results of Roentgen Ray Treatment in Patients with Hyperthyroidism*

Total number of patients.....	43
Number of patients clinically free of hyperthyroidism.....	25 (58.1%)
Number of patients markedly improved .....	8 (18.6%)
Number of patients inadequately followed .....	3 ( 6.9%)
Average basal metabolic rate before treatment (N,* 42).....	+35.7%
Average basal metabolic rate after treatment (N,* 35).....	— 2.0%
Average fall in basal metabolic rate after treatment (N,* 37).....	35.7%
Average time between first course of roentgen ray treatment and return to normal status .....	8.7 months
Average gain in weight of “cured” and improved patients (N,* 39) (34 gained; 4 lost; 1 remained same).....	11.1 lb. (5 Kg.)
Average decrease in pulse rate per minute (N,* 38) (34, decrease; 4, increase)....	20.5 beats

\* N indicates number of patients.

Twenty-five patients (or 58.1 per cent of the series) may be called “cured.” By “cured” we mean that they were clinically free of signs or symptoms of hyperthyroidism (with the exception, of course, of residual exophthalmos). Eight patients (or 18.6 per cent) were markedly improved and perhaps would have been called “cured” by many workers. Three of the patients were inadequately followed. Therefore we are unable to give their status (table 3).

The results of roentgen ray treatment would appear more impressive if we eliminated 1 patient who was treated in preparation for operation, 2 patients to whom we gave roentgen ray therapy in the hope of relieving their hyperthyroidism before they died of congestive heart failure and

3 patients who were inadequately followed. Of the remaining 37 patients, 25 (or 67.6 per cent) were "cured," 8 (or 21.6 per cent) were markedly improved and in 4 (or 10.8 per cent) the treatment failed. Thus, 33 patients (or 89.2 per cent) were either completely relieved of hyperthyroidism or were markedly improved.

Three and a half months after therapy was initiated, 2 of the patients died. One, a 74 year old man, had been in congestive heart failure for four years. Roentgen ray therapy had been undertaken in the hope of curing the hyperthyroidism before he died of heart disease. The second death occurred in a 60 year old woman who had had hyperthyroidism for over ten years and had been in congestive heart failure for two years. In her case, too, roentgen ray therapy was unable to cure the hyperthyroidism before the patient died of congestive heart failure.

The treatment of 7 patients was classified as a failure (table 4). As shown in the analysis, this classification is intentionally conservative.

TABLE 4.—"Failures" of Treatment and Complications

Number of patients in whom roentgen ray treatment failed to bring about a "cure".....	7
Number of deaths (see text).....	2
Number of patients operated on after roentgen ray treatment because of	
Severity and progression.....	1
Recurrence .....	1
Roentgen ray burn (filter left out).....	1
One course of roentgen ray therapy given preparatory to operation.....	1
Family difficulties .....	1
Complications	— 5
Roentgen ray burn (filter left out).....	1
Tracheitis and esophagitis.....	15

The first patient was a severely sick Chinaman who had been operated on eight months before and had a recurrence so severe that his metabolic rate was  $+75$  per cent. In spite of administration of iodine and two courses of roentgen ray therapy, the hyperthyroidism persisted and he became so toxic that he nearly died after a second radical thyroidectomy. Later he had characteristic myxedema. The second failure occurred in a patient who after three courses of roentgen ray therapy had shown improvement, with a decrease in the size of the thyroid to well within normal limits. She had a recurrence somewhat over a year after roentgen ray therapy was completed and was operated on because she was dissatisfied with the therapy. The remaining 5 patients whose treatment failed consisted of the 2 patients who died, a patient who was given one course of roentgen ray treatment preparatory to operation, a patient who was operated on after a roentgen ray burn on her neck (a filter had been left out during therapy) and a patient who was operated on because of a family situation which warranted treatment that would get her well as quickly as possible. It should be understood that roentgen ray therapy was given to the 2 patients who died only in the hope of saving their



lives, to the third patient only as preparation for operation and to the fourth, who in retrospect was a poor choice for this form of treatment, because certain factors in the environment had not been thoroughly appreciated. The treatment of the remaining 3 patients may be classified simply as a failure.

The statement frequently is made that achievement of a normal clinical status takes much more time by roentgen ray therapy than by subtotal thyroidectomy. For the 25 patients whom we have classified as "cured" the average length of time required for the cure was eight and seven-tenths months. By "cured" we mean afforded complete subjective relief of the symptoms of hyperthyroidism and complete objective relief as indicated by the results of physical examination, return of the basal metabolic rate to a normal level (that is, low normal) and decrease in the size of the thyroid gland to normal. The interval between onset of treatment and "cure" undoubtedly was longer than the interval before return to normal status following partial thyroidectomy in a comparable series, but certainly not inordinately so.

Nineteen of the "cured" patients had not been operated on prior to roentgen ray treatment. Fourteen of these had three courses of treatment, 1 had two and a half courses, 3 had two courses and 1 had only one course (the last patient might well have had spontaneous recovery without roentgen ray therapy). Of 6 patients with recurrences following operation, 2 had three courses and 4 had two courses of roentgen ray treatment. As one would expect, the patients who had the most thyroid tissue required the most roentgen ray treatment.

Only 22 patients of the entire series received iodine. It was administered for an average of six and nine-tenths months. Twenty-one patients, including 11 of those "cured," received no iodine at all.

The patients were followed for an average of thirty-one and four-tenths months after treatment; of course those who died or who were operated on are excluded from this group. One of those who were inadequately followed was seen for only four months, the second for only nine months and the third for only seven and a half months. All the others were observed over a minimum of fourteen months and a maximum of sixty-four and a half months after treatment. During this time 2 had recurrences. One was operated on in the status of a private patient and later probably had postoperative hypothyroidism. The second was given a third course of roentgen ray therapy and for three years has remained normal (to November 1941).

In 38 patients the thyroid decreased to normal or small normal size. A similar change has not been stressed by other writers. Nevertheless, we consider decrease of the gland to normal size an important factor in clinical improvement. In fact, it seems inconsistent that relief of hyperthyroidism should follow roentgen ray therapy if the thyroid does not

become definitely smaller. In several cases, by the time the patient was clinically free of signs and symptoms of the disease, the thyroid was so small that the observer, in spite of his ability to palpate and estimate with reasonable accuracy thyroids that weigh 20 to 25 Gm., found difficulty in outlining the gland. In cases of severe hyperthyroidism, the decrease in the size of the thyroid may lag considerably behind the clinical improvement.

We have attempted to draw some conclusions as to changes in blood pressure as well as in pulse rate and weight (table 3) in the cured and in the improved groups. There are too many sources of error in the determination of blood pressure even under relatively standardized conditions to permit a statistical appraisal. Nevertheless certain trends were noted. Thirty-eight patients showed an average fall in the systolic pressure of 11 mm. of mercury (30 showed a decrease and 8 an increase) and an average increase in the diastolic pressure of 7.5 mm. of mercury (27 showed an increase and 11 a decrease). The fall in systolic and in pulse pressure probably reflects a decrease in the cardiac output, while the increase in diastolic pressure probably coincides with an increase in arteriolar tone commensurate with the fall in the basal oxygen consumption. As already intimated, our series is too heterogeneous, especially as to age, to allow any interpretation of the changes noted except that they may be regarded as reflecting a trend.

The presence or absence of complications is worth special attention. None of the patients who received roentgen ray therapy alone later had hypothyroidism or myxedema. However, 3 of those who were operated on after roentgen ray treatment had these conditions. The handling of an ambulatory patient during the interval after roentgen ray treatment and before improvement which brings his symptoms to subclinical ranges may need to include measures that cause him to gain weight and to overcome nervousness. Thus, we have used high calory, high carbohydrate, high vitamin diets, sedatives in adequate doses, vitamin supplements (especially vitamin A and thiamine hydrochloride) and in one half of our cases iodine in small doses (in the form of compound solution of iodine U. S. P. or potassium iodide). Iodine may be useful during the first few weeks after the first course of roentgen ray therapy or it may be necessary for much longer periods for the more toxic patients.

The most difficult problems in this series were presented by the complications of tracheitis and esophagitis. They occurred in 15 patients, 1 of whom had questionable postradiation laryngitis, and undoubtedly were caused by the original method of administering roentgen rays to the thyroid through two ports anteriorly, which resulted in cross firing on the trachea and the esophagus. Mild symptoms disappeared within a week or ten days, while severe ones persisted for as long as three weeks. Since this method has been abandoned and only one port has been used,

neither complication has appeared. No telangiectasis or atrophy of the skin was noted in this series, although many patients had initial reddening of the skin and several had tanning of the neck that persisted for months to years. Only one roentgen ray burn occurred, and this was due to an unfortunate accident by which a filter was omitted. None of the patients showed any clinical evidence of damage to the parathyroids.

#### COMMENT

According to the evidence presented here and elsewhere,<sup>1</sup> roentgen therapy can destroy sufficient thyroid tissue in patients with toxic goiter to produce the same results as surgical subtotal thyroidectomy. If both surgeon and roentgenologist are thoroughly competent, one of the important considerations is the selection of the patients. We have already outlined our criteria for selection of patients for roentgen ray therapy. We believe that patients with nodular goiter (unless they have recurrences after operation) should be operated on, because neoplastic nodules cannot be distinguished from involutionary nodules by palpation through the tissues of the neck. Since such a differentiation requires histologic examination, all patients with primary toxic nodular goiter should be treated surgically. There are other considerations that have not yet been discussed. Although we have no definite proof, we are under the impression that patients who sunburn easily are also more apt to contract tracheitis and esophagitis as a complication of radiation therapy. Perhaps their mucous membranes are more sensitive than those of other patients, or the tracheitis and esophagitis may be due to more important factors, such as the angles at which the roentgen ray tubes are directed.

If for any reason subtotal thyroidectomy seems desirable or necessary after one or more courses of roentgen ray therapy, the amount of thyroid tissue left in situ should be considerably greater than is customary in thyrotoxic patients who have not received roentgen ray treatment previously, because the likelihood of subsequent myxedema is greater. The effects of the roentgen rays continue for some time after the treatment is ended.

One important group of candidates for roentgen ray therapy are patients with hyperthyroidism in whom exophthalmos constitutes a prominent part of the clinical picture and in whom measurements of the eyes demonstrate severe degrees of proptosis. One of us<sup>4</sup> has reported elsewhere that in approximately 55 per cent of one series of surgically treated patients with toxic diffuse goiter, the eyes became significantly more prominent after operation, while an increase in exophthalmos occurred in only about 20 per cent of patients treated with roentgen rays.

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4. Soley, M. H.: Exophthalmos in Patients with Various Types of Goiter, *Arch. Int. Med.* **70**:206 (Aug.) 1942.

It should be mentioned that in all such patients the eyes may appear less prominent when actually they protrude to a greater degree than they did prior to the treatment of the thyrotoxicosis. This deceptive appearance is a result of loss of the stare. Since the number of patients who have received roentgen ray therapy to the thyroid has increased, the changes in the exophthalmos deserve attention. The eyes of 22 of the series of 43 patients reported on here were measured with a Hertel (Zeiss) exophthalmometer before and after treatment, and those of 5 other patients were measured after therapy only. Six, or 27 per cent, of the 22 patients showed a progression of 1.5 mm. or more in one or both eyes, and 3, or 13.6 per cent, showed a decrease of similar magnitude. The remaining 13 patients showed no significant change. In view of the fact that the more rapid changes in thyroid function (and the consequent function of the anterior lobe of the pituitary) which accompany subtotal thyroidectomy for thyrotoxicosis may play an important role in the progression of exophthalmos, patients with severe protrusion of the eyes probably should receive roentgen ray therapy rather than surgical treatment of their thyroid condition.

Many roentgenologists believe that patients with hyperthyroidism who are to have radiation to the thyroid should not receive iodine prior to the period of treatment. This opinion is based on the fact that irradiation of the normal human thyroid has little effect on the function of the gland as observed clinically. Therefore the more abnormal or hyperplastic the thyroid the greater the expected effect of roentgen rays. Our experience does not permit confirmation or refutation of these ideas. Indeed, carefully controlled and extensive observations would be necessary to determine whether or not previous therapy with iodine diminishes the rate or the extent of destruction of thyroid tissue. Obviously, the sicker the patient the more likely he is to require a long time for recovery and temporary therapeutic measures besides roentgen ray therapy, such as administration of iodine. Consequently, the slower reaction may be attributed to the severity of the hyperthyroidism rather than to a diminished response to the same amount of radiation. On theoretic grounds, we prefer to give our patients iodine, if it is necessary at all, only after the first course of roentgen ray therapy.

#### SUMMARY

Forty-three patients with unquestioned hyperthyroidism have been treated by roentgen therapy to the thyroid. One half of these (22 patients) received iodine, while the other half (21 patients) received no iodine, in conjunction with the roentgen ray treatment. Twenty-five patients (or 58.1 per cent) were clinically free of hyperthyroidism in an average time of eight and seven-tenths months from the onset of treatment and eight (or 18.6 per cent) were markedly improved. Both

groups had a coincident decrease in the size of the thyroid to within normal limits. The average basal metabolic rate was  $+35.7$  per cent before treatment and  $-2$  per cent after treatment. Three patients were inadequately followed, and their exact status is unknown.

Two patients with congestive heart failure, which had been present for two and four years, respectively, prior to treatment, died before their hyperthyroidism could be "cured." Four patients were operated on because of failure of roentgen ray therapy and for other reasons. One patient deliberately had been given a single course as preparation for subtotal thyroidectomy.

Complications consisted of tracheitis and esophagitis in 15 patients. In order to avoid these complications, we have changed the method of therapy. Radiation to the thyroid now is given through one port anteriorly.

#### CONCLUSIONS

Roentgen ray therapy in adequate dosage is successful in bringing about subtotal destruction of the thyroid in patients with toxic diffuse goiter. In the majority it results in relief of clinical symptoms, fall of basal metabolic rate to a normal level and decrease of the thyroid to normal size.

# Progress in Internal Medicine

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## REVIEW OF NEUROPSYCHIATRY FOR 1942

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In the publication field several important events are to be recorded. A new journal has been launched; in January 1942 appeared the first number of the *Journal of Neuropathology and Experimental Neurology*. It is a quarterly, and the three numbers at hand show a high standard of work and bookmaking. The editors are to be congratulated on their production and on their courage in starting such a new project in wartime.

Another event of importance is the appearance of a book by Penfield and Erickson entitled "Epilepsy and Cerebral Localization."<sup>1</sup> This book contains more good information on fits, what they are and where they come from, than any book ever published. The point of view is that of a neurophysiologist using surgery as the chief tool, but the medical and psychologic aspects of the subject are well discussed. Experimental data in the form of careful case material are freely used, and the book is well illustrated and documented. Surgeons who work in this scientific way, looking on each operation as an experiment to be carefully recorded, have proved that they can advance certain parts of physiology, especially of neurophysiology, more than the physiologist whose observations are confined to laboratory animals.

A quite different, but also important, book is one by Lennox entitled "Science and Seizures."<sup>2</sup> This is aimed at the intelligent lay reader but is interesting reading for any physician. The social, therapeutic and hereditary aspects are particularly well handled.

After the last war Prof. Kurt Goldstein was for ten years director of a large institute for the study of brain injuries. His great experience was published in a series of papers in German. Many of these are not now available, so Goldstein, now clinical professor of neurology at Tufts Medical School, Boston, has written a book of 250 pages entitled "After Effects of Brain Injuries in War: Their Evaluation and Treat-

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1. Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

2. Lennox, W. G.: *Science and Seizures*, New York, Harper & Brothers, 1941.

ment.”<sup>3</sup> This will be most valuable for all military surgeons in a war where cerebral injury is so common. It is especially valuable because Goldstein’s point of view is not that of a narrow specialist in neurologic localization but that of a biologist and a good general physician. For example, as a neurologist he knows that certain symptoms are direct sequelae of local cerebral lesions, a motor or a visual deficit, for example, but he emphasizes that the problem is never as simple as is generally assumed. One must realize that many important symptoms are *not* the direct result of damage to a part of the brain but an expression of the struggle of the changed organism to cope with the defect. This attempt of the organism to find a new adjustment gives rise to two kinds of symptoms: The first reveals the struggle; the second reflects the tendency to build up substitute performances which allow the organism to escape the struggle. He tries to come to terms with the outer world with his new nervous setup. This seems to cause changes in his “general functions,” such as fatigability, attention and interest. Goldstein has carefully broken down these generalizations into specific reactions and has then made a diagnosis for and been able to treat patients suffering from most disturbing psychologic symptoms. More specifically, he describes methods of training and physical therapy for neurologic defects. Especially useful is the discussion of the reeducation of aphasic patients. This should be used more in civil practice for patients with aphasia from vascular lesions, who are too often given up as hopeless.

“The Central Autonomic Regulations in Health and Disease, with Special Reference to the Hypothalamus,” by Heymen R. Miller,<sup>4</sup> is a most timely and useful book; as Fulton says in the introduction,

The physiologic concept of central integration of autonomic mechanisms, and the significance of overlapping representation of somatic and autonomic levels of function, have been particularly slow to find recognition and application in clinical medicine.

In 1909 Karpus and Kreidl published their first paper on “*Gehirn und Sympathicus*”; this work started the modern investigation of cerebral control over visceral functions and opened a great field in clinical medicine. Miller has taken this thirty-three years of work, epitomized what is now known of the physiologic and anatomic aspects in three chapters and discussed clinically and physiologically, each in a chapter, the regulation of body temperature, water and minerals, metabolism, circulation,

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3. Goldstein, K.: *After Effects of Brain Injuries in War: Their Evaluation and Treatment*, New York, Grune & Stratton, Inc., 1942.

4. Miller, H. R.: *The Central Autonomic Regulations in Health and Disease, with Special Reference to the Hypothalamus*, New York, Grune & Stratton, Inc., 1942.

respiration, the gastrointestinal and the genitourinary tract, reproduction, sleep and emotions.

Gibbs and Gibbs<sup>5</sup> have published a beautiful "Atlas of Electroencephalography" showing the brain waves recorded from all sorts of common and rare cerebral disorders. Concurrent with the pictures is a good discussion that must be read to make the illustrations intelligible. Too many superficial observers have gained the idea from quick inspection that the authors have shown the typical and diagnostic electroencephalograms for all sorts of disease of the nervous system, from the varied forms of epilepsy to schizophrenia and multiple sclerosis. Many are shown, but few if any are typical; they are a great aid in diagnosis, but they are not diagnostic when taken apart from the rest of the record.

### PSYCHOSOMATICS

The war has brought with it greatly increased emotional stress both among soldiers and among civilians. Medical symptoms closely related to neurotic disturbances are becoming common in military hospitals. Although the field of psychosomatics is new under that name, it is as old as the practice of medicine. If one tries to define it, many difficulties appear. Of course, the nervous system reaches and integrates all parts of the body, and "psyche" is the highest level of this nervous system. Logically and physiologically, therefore, psychosomatics has a place in every branch of medicine. Nevertheless, common sense dictates that the term psychosomatics refers to a clinical field, recently brought into the limelight by simultaneous advances in medicine and in psychiatry, a field where advance is urgently needed because of the effects on man of the war stresses. In short, it is an area of clinical activity which attends to the physiology of the emotions, where the psychiatrist can help the general physician and vice versa.<sup>6</sup>

The recent literature on psychosomatic problems is largely made up of (a) clinical descriptions and reports that show probable relations between emotions and medical symptoms and (b) attempts to analyze

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5. Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*, Boston, the Authors, 1941.

6. The six year review of the Josiah Macy Jr. Foundation (Josiah Macy Jr. Foundation: Review by the President of Activities for the Six Years Ended December 31st, 1936, New York, 1937) devotes much space to a discussion of psychosomatic problems. One paragraph is particularly apt in this discussion:

"Investigation of these problems can best be conducted through integrated clinical, physiological and psychological studies within the various clinical branches; for until the family physician, the pediatrician and the surgeon, as well as the various specialists, understand and deal with psychosomatic problems, no real advance can be made. When they do so, the term itself will be obsolete, for the practice of medicine will have become the practice of 'psychosomatic medicine.'"



the psychologic types of the persons who fall ill with such medical diseases as asthma, hypertension, arthritis, neurodermitis, colitis and peptic ulcer. The former kind of investigation is amassing an important body of data, the latter kind is intriguing and makes good reading, but to the tough minded person it is still quite unconvincing. The psychologic descriptions are too much alike, and the diseases are too obviously different.

As regards the gastrointestinal tract, Alexander <sup>6a</sup> believes that symptoms referable to the upper part, gastric syndromes, are encountered in persons who are active, independent and efficient; persons with colonic diarrhea are dependent, with feelings of guilt and obligation, and those with constipation are stingy, accept much and give little. Other investigators <sup>7</sup> find that patients with mucous colitis are meticulous, compulsive and resentful. Even ulcerative colitis has been studied from the personality standpoint <sup>8</sup>; patients with this disorder are said to be seclusive, apathetic and dependent. One might say that these psychologic attitudes might well be the result of the illness, especially in such a severe illness as ulcerative colitis, and have no relation to causation. Most of the investigators, however, have gone into the personality study thoroughly enough to have evidence concerning the patients' psychologic traits before they had the gastrointestinal symptoms. Moreover, many have been relieved by psychiatric treatment.

The cardiorespiratory system is, if anything, more easily affected by emotions than the gastrointestinal tract. Normal emotions are expressed by heart rate and respiration; nervousness that is so common as to be hardly classed as pathologic is shown by rapid breathing, sighing, increased ventilation, rapid and irregular heart beat. Finesinger's <sup>9</sup> careful studies of respiration show that the spirogram is a delicate indicator of emotional reactions. Most patients with anxiety neurosis have an irregular spirogram with many sighs; hysterical patients usually have somewhat irregular spiograms deviating from the normal, but not as greatly as those of the anxiety group. Respiratory disorders of the most severe nature, such as asthma, seem to have psychologic com-

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6a. Alexander, F.: *Psychoanalyt. Quart.* **3**:501, 1934.

7. White, B. V.; Cobb, S., and Jones, C. M.: *Mucous Colitis: A Psychological Medical Study of Sixty Cases*, Psychosomatic Medicine Monograph, no. 1, Washington, D. C., National Research Council, 1939.

8. Daniels, G. E.: *New England J. Med.* **226**:178, 1942. Lindemann, E.: *Ulcerative Colitis*, read at the meeting of the Massachusetts Psychiatric Society, February 1942.

9. Finesinger, J. E.: *Psychosom. Med.* **2**:333, 1940.

ponents. French and Alexander and others<sup>10</sup> studied 27 cases of asthma intensively by psychoanalytic methods. They find that situations which tend to increase respiration, such as emotion, exertion and hurry, may bring on asthmatic attacks. Extreme emotion may stop the attack, perhaps because epinephrine is secreted into the blood stream. Many asthmatic patients were found to be excessively dependent on their mothers, and situations associated with separations from the mother often brought on attacks. Of course, the allergic aspect of the disease is given due consideration. It is not a matter of either allergy or emotions but a varying combination of the different factors. Greenhill and Finesinger<sup>11</sup> have found in a series of patients suffering from atopic dermatitis that exacerbation of the cutaneous lesion occurred in many cases when feelings of insecurity, hostility and depression were brought on. Saul<sup>12</sup> found that repressed and frustrated longing was an important factor in bringing on other kinds of allergic manifestations, such as rhinitis, edema and urticaria.

The role of the emotions in precipitating cardiac and circulatory crises has long been studied. Angina pectoris and hypertension are the commonest examples cited.

Rennie<sup>13</sup> believes that hypertension may be associated with protracted resentment and insecurity. Alexander<sup>14</sup> finds that hypertensive patients belong to the group of "overly inhibited, yet at the same time, intensely hostile and aggressive individuals."

In England the war has brought out a new crop of cases of neuro-circulatory asthenia (in the last war more than 40,000 men were given pensions because of this syndrome). The pendulum has swung away from the former opinion that this was an "effort syndrome" caused by overexertion in men who were soft to the opinion that the disorder is a form of anxiety neurosis. Wood<sup>15</sup> has studied a large series of cases and supports the latter theory emphatically. White<sup>16</sup> has described the syndrome briefly and rightly separates it from "cardiac neurosis," which in his terminology is the result of frightening a person about his heart when he has a harmless murmur or an insignificant valvular lesion.

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10. French, T. M.; Alexander, F., and others: *Psychogenic Factors in Bronchial Asthma*, Psychosomatic Medicine Monograph, nos. 1 and 2, Washington, D. C., National Research Council, 1941, vol. 2.

11. Greenhill, M. H., and Finesinger, J. E.: *Neurotic Symptoms and Emotional Factors in Atopic Dermatitis*, Arch. Dermat. & Syph. **46**:187 (July) 1942.

12. Saul, J.: *Psychosom. Med.* **3**:66, 1941.

13. Rennie, T. A. C.: *New England J. Med.* **221**:448, 1939.

14. Alexander, F.: *Psychosom. Med.* **1**:173, 1939.

15. Wood, P.: *Brit. M. J.* **1**:767, 805 and 845, 1941.

16. White, P. D.: *Mod. Concepts Cardiovasc. Dis.* **11**:8, 1942.

There are many angles to the problem of neurocirculatory asthenia that are not yet settled.

The effects of epinephrine on circulation and respiration have been mentioned. Other hormones are intimately associated with emotional states. Benedek and Rubenstein<sup>17</sup> have studied the correlation between ovarian activity and sex drive, fantasy and dreams. The data are all from 1 case intensively studied by endocrinologic and psychiatric methods. Although the evidence is not extensive enough to justify conclusions, a start has been made on the careful study of the relation of menstruation and emotions. Many other studies might be mentioned on arthritis, Raynaud's disease, epilepsy and hyperthyroidism. The ones discussed are from some of the more important reports published in the last three years.

#### DISORDERS OF THE EXTRAPYRAMIDAL SYSTEM

During the past six years a book<sup>18</sup> and several important papers<sup>19</sup> have appeared on the functions and lesions of the extrapyramidal motor system. These summarize and bring into understandable order a great mass of experimental and clinical work of the last thirty years. Twenty-five years ago textbooks gave no clue to the function of the basal ganglions and the associated nuclei in the forebrain and mid-brain; some authors stated that nothing was known of the function. This is remarkable because many pertinent observations had been made during the preceding fifty years,<sup>20</sup> but it is a common story in the history of medicine that scattered observations are of small value until a concatenation of events focuses interest on a subject; then a great development occurs. This happened for the basal ganglions when Alzheimer (1911), Vogt (1911), Wilson (1912) and Lewy (1912) described lesions in this region corresponding to neurologic syndromes. Then the epidemic of encephalitis in 1917 to 1922 gave such a rich and dramatic demonstration of the effects of lesions of the brainstem that by 1925 the clinicopathologic pictures were recognized and referred to the extrapyramidal system, even though the physiologic implications were

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17. Benedek, T., and Rubenstein, B. B.: *Psychosom. Med.* **1**:245 and 461, 1939.

18. *Diseases of the Basal Ganglia*, Proceedings of the Association for Research in Nervous and Mental Diseases (1940), Baltimore, Williams & Wilkins Company, 1942, vol. 21.

19. (a) Keschner, M.: *Dyskinesias*, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 10, in Tice, F.: *Practice of Medicine*, pp. 307-436. (b) Bucy, P. C.: *J. Neuropath. & Exper. Neurol.* **1**:224, 1942. (c) Putnam, T. J.: *Treatment of Unilateral Paralysis Agitans by Section of Lateral Pyramidal Tract*, *Arch. Neurol. & Psychiat.* **44**:950 (Nov.) 1940. (d) Myers, R.: *New York State J. Med.* **42**:4, 1942.

20. Hammond, W. A.: *A Treatise on the Diseases of the Nervous System*, New York, D. Appleton and Company, 1871.

confused. Before this there had been an "upper motor neuron" and a "lower motor neuron" to explain motor function. The new knowledge of brainstem function added so many intercalated motor neurons that the old idea no longer served. The "extrapyramidal syndromes" appeared. These are pseudobulbar paralysis, athetosis, dystonia, paralysis agitans, chorea, hepatolenticular degeneration (Wilson's disease) and pseudosclerosis. The typical forms of each are not difficult to recognize, but the etiologic agents are so various that many overlapping syndromes appear. This is especially true of a diffuse infection like encephalitis lethargica the manifestations of which simulate almost the whole list of syndromes.

To describe all these would be to write a textbook, and this has been recently well done by Keschner.<sup>19a</sup> For a review it is better to summarize the anatomic and the physiologic aspects and point out how lesions may interfere at different points to cause the disturbances of function one recognizes as symptoms.

#### BASAL GANGLIONS AND ALLIED STRUCTURES

Much difficulty is caused by the varied use of anatomic names in the study of this region. Lewy<sup>21</sup> has gone into the history of the nomenclature and concludes that common use at the present time makes it wise to accept the terms striatum and pallidum as signifying the two great basal ganglionic masses. There are several other nuclei nearby which are sometimes included in the term basal ganglions, the largest of these being the thalamus. The others may be said to be "peduncular" rather than "basal." Probably the best plan is to call the whole area "brainstem"<sup>22</sup> and speak of the different gray masses, or nuclei, of the brainstem, rather than to go into anatomic niceties that have little physiologic significance. Then the nuclei of the upper part of the brainstem, related to the extrapyramidal system, can be summarized as follows:

##### *Nuclei of the Upper Part of the Brainstem*

Forebrain	{	Caudate nucleus	{	putamen {striatum		
		Lenticular nucleus			{	pallidum
		Thalamus				
		Hypothalamus				
Midbrain	{	Subthalamic nucleus				
		Red nucleus				
		Reticular formation (upper part)				
		Substantia nigra				

Figure 1, taken from a recent paper in *Medicine* by Benda and Cobb,<sup>23</sup> gives an idea of the relations. The brainstem is cut through the midbrain to show the red nucleus (*R. N.*) and the substantia nigra

21. Lewy, F. H.: *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:1, 1942.

22. Rioch, D. M.: *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:133, 1942.

23. Benda, C. E., and Cobb, S.: *Medicine* **21**:95, 1942.

(*S.N.*). The nuclei of the reticular formation (*R.*) are close to these in the midbrain and extend down into the medulla. The whole of the cut-off segment of the brainstem is moved down in the diagram for visibility; normally, it is tucked up close to the striatum and the pallidum between the temporal lobes.

#### PHYSIOLOGY OF THE EXTRAPYRAMIDAL SYSTEM

From 1912 to 1934 the consensus was that the function of the striatum and the pallidum had to do with "tone," "postural tone" or, more clearly stated, the taking and maintaining of postures and the control of automatic locomotor reflexes. Then the work of Bard<sup>24</sup> and Rioch<sup>25</sup> showed that the functions of these upper levels of the brainstem were more complex, had to do with highly integrated behavior patterns and could be modified by experience. Their functions resembled what one had previously considered "cortical" functions. Posture was found to be integrated much lower down the neuraxis. In the spinal cord there is little postural activity, but the more highly integrated spinal movements have simple elements of posture held for a short time if the stimulus is maintained. In the hindbrain are important postural mechanisms which cause slow and prolonged muscular responses. Chief among these is the vestibular apparatus, especially the lateral vestibular nucleus (Deiters'). This maintains a steady contraction of the antigravity muscles, holding man in the standing position. Modifications of this may be brought about by the neck reflexes which have as their afferent stimuli the proprioceptive impulses from the muscles of the neck innervated by the upper cervical and the spinal accessory nerves. Righting reflexes, that aid animals to arise and keep upright, are controlled largely from the midbrain (subthalamic nucleus, substantia nigra, red nucleus and reticular formation). For example, the eyes, working on midbrain mechanisms and in coordination with the hindbrain, set up a train of reflex events which brings a prone animal first to look up, then to sit up and then to stand, in quick and smooth sequence. The next level of the motor system lies in the striatum. Mammals with the cerebral cortex removed and the basal ganglions intact can walk, run and even jump in an effective, though automatic, way. All they seem to lack is initiative, spontaneity and memory. In other words, they have few and rudimentary conditioned reflexes and do not react in the light of past experience. Such an animal is able to go about but has no direction as to where to go except when immediate strong stimuli are applied.

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24. Bard, P.: *Psychol. Rev.* **31**:309 and 424, 1934.

25. Rioch, D. M.: *Psychiatry* **1**:339, 1938.

A decorticate cat, even when the striatum is injured, can perform all the locomotor functions, so it is the peduncular nuclei rather than the striatum and the pallidum that must be concerned with simple locomotion. The function of the striatum is probably to elaborate motor behavior of even the more highly integrated types and thus make it smooth and effective. The observations of Akelaitis, von Wagenen and associates, cited by Smith and Akelaitis,<sup>26</sup> are pertinent here. They sectioned the corpus callosum in several cases and found no loss of motor skill. In 2 patients, both stenographers, the entire corpus callosum was cut, yet after operation they had lost none of their skill as typists, a special motor performance which needs the closest cooperation between the left and the right hand. Also among the patients was a pianist, who lost none of her skill after the operation. With the corpus callosum gone it seems that the coordination must have been carried out in the striatum or possibly even lower ganglions.

The basal ganglions may function well in decorticated mammals, but normally in human beings they are closely connected with the "extrapyramidal" part of the cerebral cortex, areas 6 and 8 of Brodman (see figure 1). Area 4 is recognized histologically by the presence of the giant pyramidal cells of Betz. The giant cells of area 4 send fibers mostly to the spinal levels of the opposite side. Stimulation of area 4 causes remarkably local contraction in small muscle groups or even single muscles. In area 6 electrical stimulation results in much more complex, slow, postural movements, involving more muscle groups. The fibers from cells in this area end mostly in area 4 and the basal ganglions (fig. 1).

Cortical area 6 is the highest level of the extrapyramidal system and controls the striatum and to some extent cortical cells in area 4. Motor skills learned by means of the cortex can probably be relegated to the striatum when they become automatic. The neostriatum elaborates and smoothes out the coarser motor integrations of the paleostriatum. These in turn control the primitive walking reflexes of the subthalamic region, which make use of the righting reflexes of the midbrain nuclei and the antigravity reflexes of the hindbrain from the lateral vestibular nucleus. The lowest level is, of course, the spinal, where all the extrapyramidal impulses (running down the vestibulospinal, reticulospinal and rubrospinal tracts) reach the "motor pool" about the ventral horn cells and eventually discharge along the final common path. This summary is not entirely accurate because there are such unexplained exceptions as

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26. Smith, K. V., and Akelaitis, A. J.: Studies on Corpus Callosum, *Arch. Neurol. & Psychiat.* **47**:519 (April) 1942.

the finding that a few "extrapyramidal" fibers come from area 6 and, joining those from area 4, travel down through the pyramids of the medulla oblongata and hence are "pyramidal."

One would not expect to have refined localization of function in such a mechanism as the basal ganglions, where the main work is probably

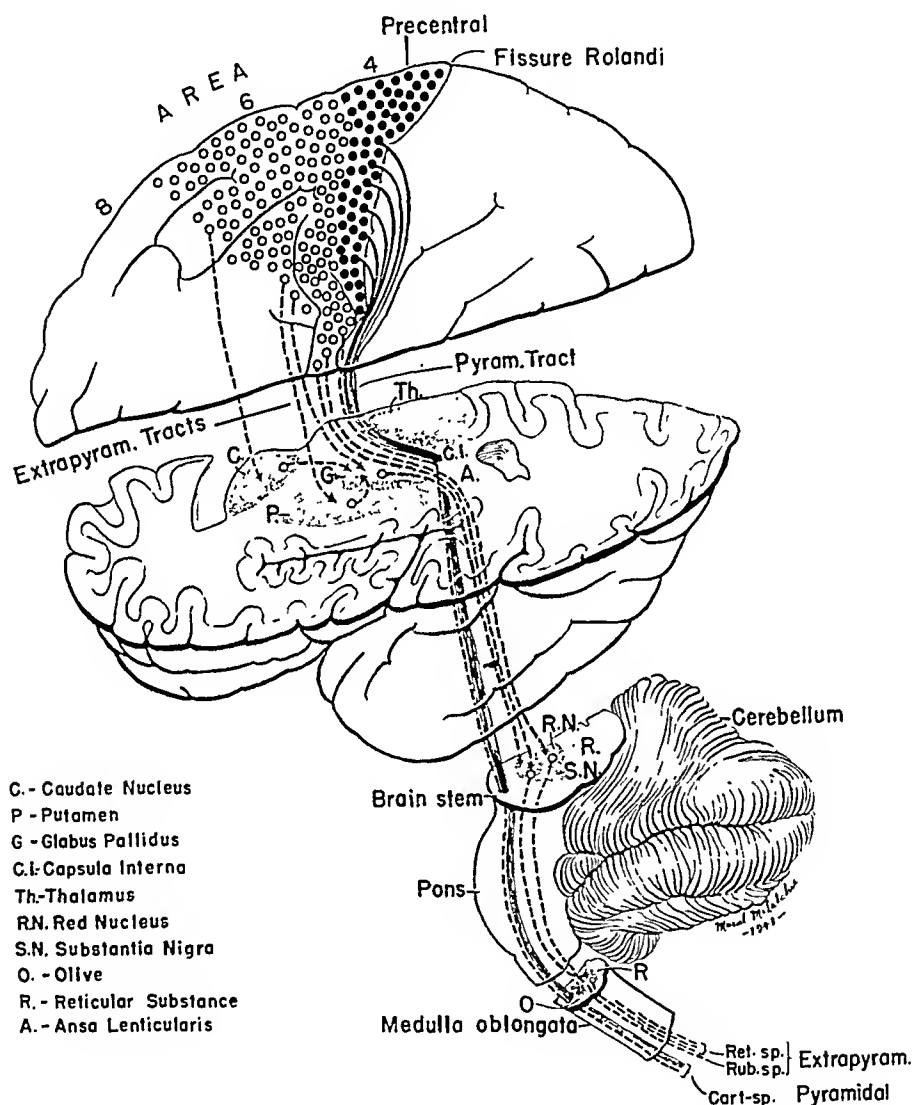


Fig. 1.—Diagrammatic sketch of the pyramidal and the extrapyramidal motor systems after Benda and Cobb.<sup>23</sup>

integrating, elaborating and smoothing out motor acts which vary all the way from learned skills that have become automatic to rather simple locomotor performances. The evidence from lesions sustains this expectation; localization is probably rather general in distribution; for example, the right half of the ganglionic complex controls the left half of the body. Certain symptoms appear when certain parts of the complex

are injured. When the subthalamic nucleus is affected by a focal lesion, the opposite arm and leg may show the violent, rhythmic, flail-like movements known as "ballismus." Tremor of the Parkinson type occurs when the substantia nigra, the pallidum and cortical area 6 are injured, but not destroyed, and the pyramidal tract is functioning.<sup>23</sup> Athetosis usually results from lesions of the striatum or the precentral cortex or both.<sup>19b</sup> Chorea minor probably comes from scattered petechial lesions in the striatum and the cortex, while the chronic chorea of old age has a widespread degeneration of the striatum, the pallidum and the cortex. The rigidity of paralysis agitans is sometimes laid to a lesion of the pallidum.

Of course, such observations as the foregoing ones only give a rough indication of the function. They show what the rest of the organization can and does do when a certain nucleus or group of nuclei drop out. Some clinicopathologic investigators have tried to go farther and localize more exactly the representation of the limbs and functions. At the present time the evidence does not seem to justify such refinement. Experimental work on animals has been of little help, largely because of the fact that only the higher apes have motor functions that resemble those of man.

#### THERAPY OF INVOLUNTARY MOVEMENTS

Of the various types of spasm and tremor the only one that appears to be amenable to reeducational training is athetosis. This may be because it occurs frequently in youth as the result of birth injury. Patient work with athetoid children over years has often made their lives much more bearable but has rarely made them self-supporting.<sup>27</sup>

Treatment by the use of drugs is of little value in torticollis, athetosis, torsion spasm and ballismus; it is most helpful in chorea and paralysis agitans. In chorea sedatives, such as phenobarbital, have been effective, and fever therapy seems to have been of benefit in many cases.<sup>28</sup> Paralysis agitans is rarely relieved by sedatives, although a combination of phenobarbital with belladonna sometimes is more beneficial than either compound alone. The best drugs for the tremor, rigidity and ocular and leg spasms of paralysis agitans are those of the atropine group. Recent experience has shown that no one alkaloid is as effective as a combination of both atropine and scopolamine. That is why extracts of belladonna root have better effects than the pure drugs. For some time

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27. Carlson, E. R.: *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:534, 1942.

28. Barnacle, C. H.; Ewalt, J. R., and Ebaugh, F. G.: *Artificial Fever Treatment of Chorea: Preliminary Report, J. A. M. A.* **106**:2046 (June 13) 1936.



there was supposed to be a magic in the Bulgarian root, but that myth has been dispelled by the success of American products that contained both alkaloids. It is important to push the drug employed until visual disturbances and dry mouth cause one to stop; then stay at that dose until tolerance is increased, and after a week or two push the dose higher in order really to ease the rigidity and stop the tremor. Special eye glasses can be made to help vision; frequent sips of lemon juice or vinegar in water help the dry mouth. Syntropan<sup>29</sup> has a less toxic effect in moderate doses.

The addition of amphetamine sulfate to one of the atropine group of drugs is effective in some cases. It gives the patient more motor initiative and speeds up motor performance, as well as improving the mood. Five milligram doses administered at 7 a. m., 11 a. m. and 3 p. m. with the appropriate dose of fluidextract of belladonna root will usually suffice. The drug should not be given in excess or after 3 p. m., because of its marked effect in preventing sleep. In some cases one dose of 10 mg. on arising is better, but this compound sometimes causes a feeling of nervous tension with increased tremor and so must be avoided. Only a trial will tell which patient will be benefited.

Surgical treatment of the involuntary movements resulting from disease of the basal ganglions has taken a new start in the last five years because of the advances in knowledge of the physiology of these ganglions and their connections with the motor cortex. Horsley<sup>30</sup> as early as 1890 successfully extirpated part of the precentral gyrus (probably area 6) for athetosis. The cutting of the first three cervical anterior roots and the spinal accessory nerve for spasmodic torticollis is now a well recognized procedure, with good results.<sup>31</sup> The recent operations for athetosis, tremor and spasms, according to Putnam,<sup>32</sup> have

. . . resulted in a fairly high mortality, and in many failures, but also in a gratifying number of dramatic successes. There is much reason for hoping that the worst is now over, and that the future will see indications clearly defined and procedures standardized and accepted. The urgent need for relief in the many severe cases of dystonia and parkinsonism should impel us to waste no opportunity for advance.

Myers<sup>33</sup> divides these surgical procedures into operations (a) at the level of the spinal cord, (b) at the level of the cerebellomesencephalic

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29. Schlezinger, N. S., and Alpen, B. J.: *Am. J. M. Sc.* **201**:374, 1941.

30. Horsley, V.: *Brit. M. J.* **2**:1286, 1890.

31. Foerster, O.: *Zentralbl. f. Chir.* **1**:402, 1920; **2**:1106, 1920. Dandy, W. E.: *Operation for Treatment of Spasmodic Torticollis*, *Arch. Surg.* **20**:1021 (June) 1930.

32. Putnam, T. J.: *A. Research Nerv. & Ment. Dis.*; *Proc.* (1920) **21**:666, 1942.

33. Myers, R.: *A. Research Nerv. & Ment. Dis.*, *Proc.* (1940) **21**:614, 1942.

complex, (*c*) at the level of the cerebral cortex and (*d*) at the level of the basal ganglions (see figure 1). Putnam<sup>32</sup> has cut the anterolateral or lateral tracts in the cervical portion of the spinal cord in 42 patients with athetosis. The results have been excellent in case of unilateral disease, but of the patients with bilateral athetosis, only about half have had much relief. The operative mortality has been less than 12 per cent. Putnam has tried lateral cordotomy for paralysis agitans in 7 instances. Here, as in athetosis, it is the patients with unilateral disease who were most relieved.

Operations at the cerebellomesencephalic level are particularly dangerous, and results so far do not justify this approach.

About thirty operations have been performed at the level of the basal ganglions, mostly by Myers. Parts of the caudate and the lenticular nucleus have been removed, but the most effective operation is the cutting of the fasciculus and ansa lenticularis (the main efferent pathway of the pallidum and the striatum) as they pass near the foramen of Monro beneath the floor of the lateral ventricle (see figure 1). The approach is through an incision in the frontal lobe that exposes the floor of the lateral ventricle and the foramen of Monro. Several patients have been remarkably improved by this procedure, even those with bilateral involvement who have had bilateral operations. Unfortunately, the patients are usually poor "operative risks," the operation is difficult and the mortality is about 20 per cent. Obviously, the physiologic approach is correct, but Myers himself believes the operative procedure needs refinement before it should be continued. Extirpations at the cortical level (areas 4 or 6, separately or combined) have been performed for athetosis and paralysis agitans. The patients with unilateral symptoms, especially those with conditions of traumatic origin, have usually been relieved.<sup>34</sup> In patients with degenerative disease of both hemispheres, double athetosis and Parkinson's disease, the results are more dubious and the mortality is high, over 17 per cent.<sup>35</sup>

One must conclude that at present the operative treatment of involuntary movements is experimental. Much headway has been made; much has been learned about the physiologic and pathologic aspects, and the prospects are bright that in the not far distant future surgical intervention will make a great contribution to the treatment of athetosis, tremor, rigidity, torsion spasm, ballismus and chorea, as it has already done for torticollis and the rare cases of unilateral dyskinesia. It must be

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34. Bucy, P. C.: *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:551, 1942.

35. Klemme, R. M.: *A. Research Nerv. & Ment. Dis., Proc.* (1940) **21**:596, 1942.

acknowledged, however, that up to the present no relatively simple and safe operation has been devised that offers adequate hope of relief of symptoms.

#### ELECTROENCEPHALOGRAPHY

Since 1935, when the very beginnings of clinical electroencephalography were mentioned in this review, conspicuous advance has been made. Now many large hospitals are equipped to make electroencephalographic records ("brain waves"), and in certain spheres of neurology the technic has become an important diagnostic aid. The fine atlas of Gibbs and Gibbs<sup>5</sup> already mentioned is an extensive study, showing that an abnormal electroencephalogram accompanies most lesions of the cerebrum and some disorders in which lesions are not evident at autopsy. The brain wave pattern, however, is not characteristic for any disease, with the exception of the bursts of wave-spike formations frequently seen in epilepsy, usually in petit mal. This fact, however, does not nullify the usefulness of the electroencephalogram as a diagnostic instrument. Often one wishes to know whether certain symptoms are caused by cerebral lesions or are due to neurotic or psychotic disorders without lesions. For example, a differential diagnosis between schizophrenic stupor and coma due to brain tumor would be possible. Again, a hysterical fit can be differentiated from an epileptic seizure if one is careful to rule out the fast high waves caused by movements of muscle.

Localization of cerebral lesions can also be made electrically with a fair degree of accuracy. As many as twenty-four leads can be placed on the skull, and by a triangulation survey the point from which the abnormal waves seem to originate can often be found. This is especially useful in studying tumors and traumatic lesions and in deciding whether an epilepsy is focal and perhaps approachable by surgical therapy.

In psychiatry the electroencephalogram is of some diagnostic help. Manic-depressive and schizophrenic patients often show irregular unstable patterns,<sup>36</sup> but they are far from pathognomonic; some normal people show them also. Possibly phlegmatic persons show more alpha waves (about 10 per second activity over the occipital lobes), and tense, anxious persons show more rapid, small (beta) waves (see figure 2). Problem children in whom encephalopathy or epilepsy was not suspected can often be proved to be suffering from one or both of these conditions by the finding of long, slow (delta) waves. These occur normally in infancy or in deep sleep but are distinctly pathologic in children over 8 years of age who are awake.

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36. Pacella, B. L., and Barerra, S. E.: *Psychiatric Quart.* **15**:407, 1941.

Epileptic brain waves have been extensively studied, especially by Gibbs, Gibbs and Lennox<sup>37</sup> and by Jasper, in a chapter in a book by Penfield and Erickson.<sup>1</sup> The essential abnormalities are the great magnitude and the episodic nature of the discharges. The waves are large (high voltage) and come in bursts, whether they are long slow delta waves, rapid high spikes or wave-spike combinations. Epilepsy is so varied in its phenomena that there is no definite correspondence between the different types of seizure and the different sorts of epileptic wave pattern, with the exception of the common finding of bursts of wave-spike combinations in the short lapses known as petit mal. The electroencephalogram is useful not only for the diagnosis of epilepsy but in the treatment of epilepsy,

## BRAIN WAVE PATTERNS

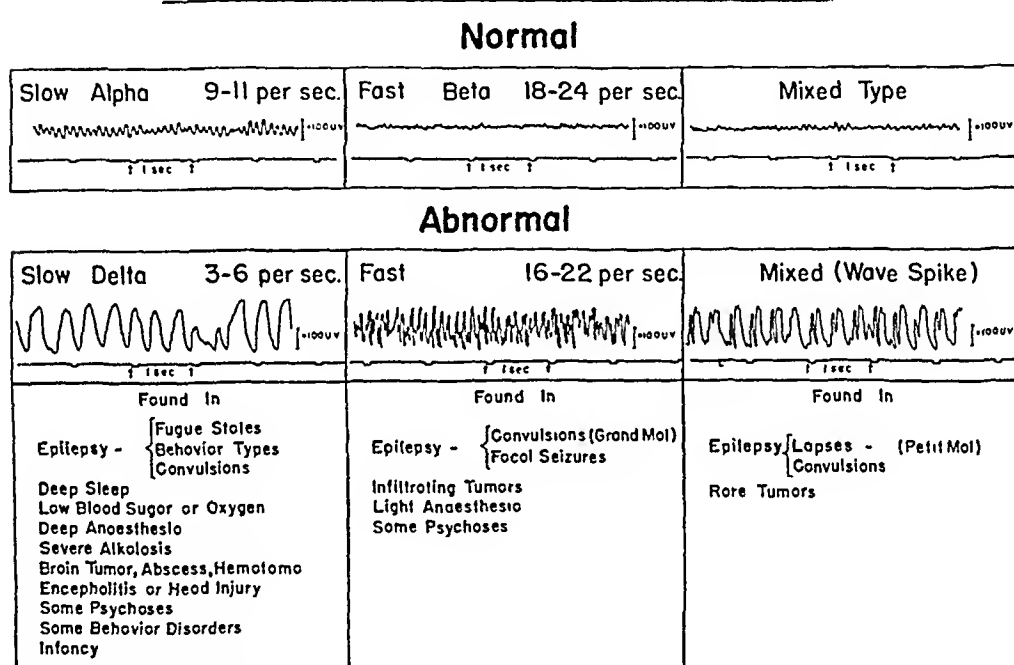


Fig. 2.—Schwab's<sup>39</sup> comparison of the more common patterns of normal and abnormal brain waves. In the abnormal group epilepsy gives the highest voltages (biggest "waves"), and they come in attacks. Sleep, coma, tumor, encephalitis, etc., are likely to have more continuous abnormal waves of less extreme voltage. Of course, the long, slow waves of sleep are a normal phenomenon and are classed under "abnormal" on the chart only because such waves would be very abnormal if produced by a person during a regular electroencephalographic test while awake.

because the effect of drugs may be followed by making repeated electroencephalograms and seeing which drug has the most effect in smoothing

37. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, *Arch. Neurol. & Psychiat.* **39**:298 (Feb.) 1938.

out the abnormal waves. In this way many weeks or months may be saved because the clinical observation of epileptic patients is a long, drawn-out affair.

Lennox<sup>2</sup> calls epilepsy "paroxysmal cerebral dysrhythmia." From the electroencephalographic point of view this is a good description and saves one from using the socially unacceptable word "epilepsy." An abnormal shower of brain waves, however, does not cause an epileptic fit, any more than abnormal electrocardiographic waves cause angina pectoris. If one wishes to speak accurately about causation, it is necessary to go back to some processes behind both the fit and the dysrhythmia. The nerve impulse and the electrical change in potential (registered as a brain wave) are not identical. Just what the nerve impulse may be is not yet known, but it is a physiologic process with characteristics quite different from an electrical current. The brain, when functioning, produces changes in electrical potential, and these are recorded in the electroencephalogram, but this is not a record of nerve impulses. Some disorganization of the nerve impulses precipitates both the clinical fits seen and the brain waves registered. The ultimate cause is physiochemical and is unknown.

Davis<sup>38</sup> has reviewed the uses of the electroencephalogram, and Schwab<sup>39</sup> has emphasized the main types of abnormality and their similarities to normal electroencephalographic phenomena. His diagram is reproduced here. Schwab's emphasis is a good corrective for the too prevalent idea that now the diagnosis of neuropsychiatric disorders is made easy because abnormal brain waves are differentially diagnostic.

Briefly stated, the electroencephalogram can record gross disorders of the function of the brain; the subtler changes are not shown or at least are not yet recognized. The abnormal brain waves can often be correlated with clinical and with autopsy data. This makes it probable that the abnormal waves are frequently related to cerebral lesions, but physiologically speaking, the electroencephalogram registers only functional changes in the brain.

Massachusetts General Hospital.

38. Davis, H.: *Electroencephalography*, J. A. M. A. **117**:983 (Sept. 20) 1941.

39. Schwab, R. S.: *M. Clin. North America* **25**:1477, 1941.

# OBESITY

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## DEFINITION

Obesity is that condition in which the body contains an abnormally large amount of adipose tissue. The excessive fat may be evenly distributed or may be present to a much greater extent in some regions than in others. When the accumulation is sharply localized to one or more discrete encapsulated masses, one speaks of "lipomatosis" in contradistinction to "obesity."

## WEIGHT

Since the accumulation of adipose tissue causes a corresponding increase in weight, much effort has been directed toward establishing a weight which is best in regard to longevity and mental and physical fitness.

*Normal Weight.*—The Child Health Association has compiled tables (tables 1 through 4) that give the average weight for height and sex of large numbers of healthy children from birth through the age of 18 years. These tables are widely accepted as the most satisfactory standards.

However, Fisk<sup>1</sup> has shown that the average weights of persons over 30 years of age are too great as judged by life expectancy and has found that the average weight at 30 is the most desirable weight for the remainder of the life. Table 5, compiled by Fisk, is based on that principle. The heights include shoes, and the weights, clothes and food.

Departures from these standards are sometimes condoned because of supposedly heavy bones, excessive muscular development or hereditary type, but according to Fisk, "Life insurance experience has shown that heavyweights, regardless of type and heredity, show an extra mortality."

*Hazard of Overweight.*—Dublin and Lotka<sup>2</sup> have analyzed the influence of weight on the duration of life of 192,304 men aged 21 years

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1. Fisk, E. L.: Health Building and Life Extension, New York, The Macmillan Company, 1923.

2. Dublin, L. I., and Lotka, A. J.: Length of Life, New York, The Roland Press Co., 1936.

or over when accepted for life insurance. The deaths per hundred thousand, age being disregarded, are given in table 6.

Dublin and Lotka concluded that "the penalty of overweight is one-fourth to three-fourths excess in mortality." These studies become still more informative when they are related to age, since excessive weight carries a much greater risk in persons beyond 45 years of age than earlier (table 7). How great the risk is for the important years from 45 to 50 appears dramatically in table 8. It is startling to learn

TABLE 1.—*Weights of Girls from Birth to School Age*

Height, In.	Weight, Lb.											
	1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	48 Mo.	60 Mo.	72 Mo.
20	8	..	..	..	..	..	..	..	..	..	..	..
21	9	10	..	..	..	..	..	..	..	..	..	..
22	10	11	..	..	..	..	..	..	..	..	..	..
23	11	12	13	..	..	..	..	..	..	..	..	..
24	12	13	14	14	..	..	..	..	..	..	..	..
25	13	14	15	15	..	..	..	..	..	..	..	..
26	..	15	16	17	17	..	..	..	..	..	..	..
27	..	16	17	18	18	..	..	..	..	..	..	..
28	..	..	19	19	19	19	..	..	..	..	..	..
29	..	..	19	20	20	20	..	..	..	..	..	..
30	..	..	21	21	21	21	21	..	..	..	..	..
31	..	..	..	22	22	23	23	23	..	..	..	..
32	..	..	..	..	23	24	24	24	25	..	..	..
33	..	..	..	..	..	25	25	25	26	..	..	..
34	..	..	..	..	..	26	26	26	27	..	..	..
35	..	..	..	..	..	29	29	29	29	29	..	..
36	..	..	..	..	..	..	30	30	30	30	31	..
37	..	..	..	..	..	..	31	31	31	31	32	..
38	..	..	..	..	..	..	..	33	33	33	33	..
39	..	..	..	..	..	..	..	34	34	34	34	34
40	..	..	..	..	..	..	..	..	35	36	36	36
41	..	..	..	..	..	..	..	..	..	37	37	37
42	..	..	..	..	..	..	..	..	..	39	39	39
43	..	..	..	..	..	..	..	..	..	40	41	41
44	..	..	..	..	..	..	..	..	..	..	42	42
45	..	..	..	..	..	..	..	..	..	..	..	45
46	..	..	..	..	..	..	..	..	..	..	..	47
47	..	..	..	..	..	..	..	..	..	..	..	50
48	..	..	..	..	..	..	..	..	..	..	..	52

that a mere 25 pounds (11 Kg.) of extra weight lessens one's life expectancy by 25 per cent. Fisk found likewise that persons in full middle life who weigh 20 pounds (9 Kg.) more than the average instead of 10 pounds (4.5 Kg.) less are incurring an extra 25 per cent risk. In another place he pointed out that "fifty pounds overweight at age forty-five imposes as much extra mortality as valvular heart disease."

#### ETIOLOGY OF OBESITY

*Is There a Disorder of the Utilization of Energy?*—Because of the prevalence of the belief that some patients gain weight even though they do not overeat and that others do not lose when they are underfed,

there has been a continued search for some metabolic aberration in this disease.

*Basal Metabolism.*—Early students found that pound for pound obese persons produce less heat in the resting postabsorptive state than do normal controls. Had they made the comparison on the basis of height, they would have found that the heat production of obese persons was greater than normal. But Rubner, Lusk and others have demonstrated that the basal heat production of all mammals is proportional to

TABLE 2.—*Weights of Boys from Birth to School Age*

Height, in.	Weight, Lb.											
	1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	48 Mo.	60 Mo.	72 Mo.
20	8	..	..	..	..	..	..	..	..	..	..	..
21	9	10	..	..	..	..	..	..	..	..	..	..
22	10	11	..	..	..	..	..	..	..	..	..	..
23	11	12	13	..	..	..	..	..	..	..	..	..
24	12	13	14	..	..	..	..	..	..	..	..	..
25	13	14	15	16	..	..	..	..	..	..	..	..
26	..	15	17	17	18	..	..	..	..	..	..	..
27	..	16	18	18	19	..	..	..	..	..	..	..
28	..	..	19	19	20	20	..	..	..	..	..	..
29	..	..	20	21	21	21	..	..	..	..	..	..
30	..	..	22	22	22	22	22	..	..	..	..	..
31	..	..	..	23	23	23	23	24	..	..	..	..
32	..	..	..	24	24	24	25	25	..	..	..	..
33	..	..	..	..	26	26	26	26	26	..	..	..
34	..	..	..	..	..	27	27	27	27	..	..	..
35	..	..	..	..	..	29	29	29	29	29	..	..
36	..	..	..	..	..	..	30	31	31	31	..	..
37	..	..	..	..	..	..	32	32	32	32	32	..
38	..	..	..	..	..	..	..	33	33	33	34	..
39	..	..	..	..	..	..	..	35	35	35	35	..
40	..	..	..	..	..	..	..	..	36	36	36	36
41	..	..	..	..	..	..	..	..	..	38	38	38
42	..	..	..	..	..	..	..	..	..	39	39	39
43	..	..	..	..	..	..	..	..	..	41	41	41
44	..	..	..	..	..	..	..	..	..	..	43	43
45	..	..	..	..	..	..	..	..	..	..	45	45
46	..	..	..	..	..	..	..	..	..	..	..	48
47	..	..	..	..	..	..	..	..	..	..	..	50
48	..	..	..	..	..	..	..	..	..	..	..	52
49	..	..	..	..	..	..	..	..	..	..	..	52

the surface area of the body and that no such relation exists when either weight or height alone is used as the basis of comparison.

Benedict, using the statistical method, has published tables by which one can predict the basal metabolic rate of normal persons on the basis of age, height and weight. His values closely approximate those calculated by the surface area method. There is, then, no doubt about the range of basal heat production of normal adults.

Subsequently, Boothby and Sandiford<sup>3</sup> measured basal heat production in 94 obese patients and found that in 81 per cent of them the rates

3. Boothby, W. M., and Sandiford, I.: J. Biol. Chem. 54:783, 1922.



were within 10 per cent of the normal heat production per square meter. In 3 instances the rates fell between —16 and —20 per cent, and another patient produced heat at a rate more than 16 per cent above normal.

✓ Strouse, Wang and Dye<sup>4</sup> compared the basal metabolic rates of normal persons with those of subjects who were underweight and over-

TABLE 3.—*Weights of Girls from Five to Eighteen Years*

Height, In.	Weight, Lb.														
	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	16 Yr.	17 Yr.	18 Yr.	
38	33	33	..	..	..	..	..	..	..	..	..	..	..	..	
39	34	34	..	..	..	..	..	..	..	..	..	..	..	..	
40	36	36	36	..	..	..	..	..	..	..	..	..	..	..	
41	37	37	37	..	..	..	..	..	..	..	..	..	..	..	
42	39	39	39	..	..	..	..	..	..	..	..	..	..	..	
43	41	41	41	41	..	..	..	..	..	..	..	..	..	..	
44	42	42	42	42	..	..	..	..	..	..	..	..	..	..	
45	45	45	45	45	45	..	..	..	..	..	..	..	..	..	
46	47	47	47	48	48	..	..	..	..	..	..	..	..	..	
47	49	50	50	50	50	50	..	..	..	..	..	..	..	..	
48	..	52	52	52	52	53	53	..	..	..	..	..	..	..	
49	..	54	54	55	55	56	56	..	..	..	..	..	..	..	
50	..	56	56	57	58	59	61	62	..	..	..	..	..	..	
51	..	..	59	60	61	61	63	65	..	..	..	..	..	..	
52	..	..	63	64	64	64	65	67	..	..	..	..	..	..	
53	..	..	66	67	67	68	68	69	71	..	..	..	..	..	
54	..	..	..	69	70	70	71	71	73	..	..	..	..	..	
55	..	..	..	72	74	74	74	75	77	78	..	..	..	..	
56	..	..	..	..	76	78	78	79	81	83	..	..	..	..	
57	..	..	..	..	80	82	82	82	84	88	92	..	..	..	
58	..	..	..	..	..	84	86	86	88	93	96	101	..	..	
59	..	..	..	..	..	87	90	90	92	96	100	103	104	..	
60	..	..	..	..	..	91	95	95	97	101	105	108	109	111	
61	..	..	..	..	..	..	99	100	101	105	108	112	113	116	
62	..	..	..	..	..	..	104	105	106	109	113	115	117	118	
63	..	..	..	..	..	..	..	110	110	112	116	117	119	120	
64	..	..	..	..	..	..	..	114	115	117	119	120	122	123	
65	..	..	..	..	..	..	..	118	120	121	122	123	125	126	
66	..	..	..	..	..	..	..	..	124	124	125	128	129	130	
67	..	..	..	..	..	..	..	..	128	130	131	133	133	135	
68	..	..	..	..	..	..	..	..	131	133	135	136	138	138	
69	..	..	..	..	..	..	..	..	..	135	137	138	140	142	
70	..	..	..	..	..	..	..	..	..	136	138	140	142	144	
71	..	..	..	..	..	..	..	..	..	138	140	142	144	145	

weight. Per square meter of body surface they found practically no differences.

✓ Among 180 cases of extreme obesity Grafe<sup>5</sup> found only 3 in which there was a definite decrease in basal metabolic rate.

4. Strouse, S.; Wang, C. C., and Dye, M.: Studies on Metabolism of Obesity: Basal Metabolism, Arch. Int. Med. 34:275 (Sept.) 1924.

5. Grafe, E.: Metabolic Diseases and Their Treatment, translated by M. G. Boise, Philadelphia, Lea & Febiger, 1933.

TABLE 4.—*Weights of Boys from Five to Nineteen Years*

Height, In.	Weight, Lb.														
	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	16 Yr.	17 Yr.	18 Yr.	19 Yr.
38	34	34	..	..	..	..	..	..	..	..	..	..	..	..	..
39	35	35	..	..	..	..	..	..	..	..	..	..	..	..	..
40	36	36	..	..	..	..	..	..	..	..	..	..	..	..	..
41	38	38	38	..	..	..	..	..	..	..	..	..	..	..	..
42	39	39	39	39	..	..	..	..	..	..	..	..	..	..	..
43	41	41	41	41	..	..	..	..	..	..	..	..	..	..	..
44	44	44	44	44	..	..	..	..	..	..	..	..	..	..	..
45	46	46	46	46	46	..	..	..	..	..	..	..	..	..	..
46	47	48	48	48	48	..	..	..	..	..	..	..	..	..	..
47	49	50	50	50	50	50	..	..	..	..	..	..	..	..	..
48	..	52	53	53	53	53	..	..	..	..	..	..	..	..	..
49	..	55	55	55	55	55	55	..	..	..	..	..	..	..	..
50	..	57	58	58	58	58	58	58	..	..	..	..	..	..	..
51	..	..	61	61	61	61	61	61	..	..	..	..	..	..	..
52	..	..	63	64	64	64	64	64	64	..	..	..	..	..	..
53	..	..	66	67	67	67	67	68	68	..	..	..	..	..	..
54	..	..	..	70	70	70	70	71	71	72	..	..	..	..	..
55	..	..	..	72	72	73	73	74	74	74	..	..	..	..	..
56	..	..	..	75	76	77	77	77	78	78	80	..	..	..	..
57	..	..	..	..	79	80	81	81	82	83	83	..	..	..	..
58	..	..	..	..	83	84	84	85	85	86	87	..	..	..	..
59	..	..	..	..	..	87	88	89	89	90	90	90	..	..	..
60	..	..	..	..	..	91	92	92	93	94	95	96	..	..	..
61	..	..	..	..	..	..	95	96	97	99	100	103	106	..	..
62	..	..	..	..	..	..	100	101	102	103	104	107	111	116	..
63	..	..	..	..	..	..	105	106	107	108	110	113	118	123	127
64	..	..	..	..	..	..	..	109	111	113	115	117	121	126	130
65	..	..	..	..	..	..	..	114	117	118	120	122	127	131	134
66	..	..	..	..	..	..	..	..	119	122	125	128	132	136	139
67	..	..	..	..	..	..	..	..	124	128	130	134	136	139	142
68	..	..	..	..	..	..	..	..	..	134	134	137	141	143	147
69	..	..	..	..	..	..	..	..	..	137	139	143	146	149	152
70	..	..	..	..	..	..	..	..	..	143	144	145	148	151	155
71	..	..	..	..	..	..	..	..	..	148	150	151	152	154	159
72	..	..	..	..	..	..	..	..	..	..	153	155	156	158	163
73	..	..	..	..	..	..	..	..	..	..	157	160	162	164	167
74	..	..	..	..	..	..	..	..	..	..	160	164	168	170	171

TABLE 5.—*Ideal Weights of Men and Women\**

Men			Women		
Height		Weight, Lb.	Height		Weight, Lb.
Ft.	In.		Ft.	In.	
5		126	4	8	112
5	1	128	4	9	114
5	2	130	4	10	116
5	3	133	4	11	118
5	4	136	5		120
5	5	140	5	1	122
5	6	144	5	2	124
5	7	148	5	3	127
5	8	152	5	4	131
5	9	156	5	5	134
5	10	161	5	6	138
5	11	166	5	7	142
6		172	5	8	146
6	1	178	5	9	150
6	2	184	5	10	154
6	3	190	5	11	157
6	4	196	6		161
6	5	201			

\* Adapted from Fisk.<sup>1</sup>

The occasional moderately low rate (from — 15 to — 25 per cent) exhibited by an obese person does not contribute to the understanding of obesity, since equally low rates are encountered as frequently among healthy persons.

The few obese persons whose basal metabolic rate is low enough to be definitely pathologic will be found to be suffering from some

TABLE 6.—*Influence of Weight on Mortality; Deaths per Hundred Thousand Men Accepted for Insurance*

Weight	Deaths
Standard.....	844
Underweight, total.....	848
Overweight, total.....	1,111
Underweight, 5-14%.....	833
Underweight, 15-34%.....	913
Overweight, 5-14%.....	1,027
Overweight, 15-24%.....	1,215
Overweight, 25% or more.....	1,472

TABLE 7.—*Influence of Weight on Mortality as Modified by Age, Deaths per Hundred Thousand*

Weight	Age, Yr.	
	Under 45	Over 45
Standard.....	463	1,308
Underweight, total.....	498	1,274
Overweight, total.....	527	1,824

TABLE 8.—*Influence of Overweight on Mortality in Persons Aged 45 to 50 Years*

Pounds Overweight	Increase in Death Rate Over Average, %
10 .....	8
20 .....	18
30 .....	28
40 .....	45
50 .....	58
60 .....	67
70 .....	81
90 .....	116

disease in which adiposity is a complication or an unrelated accompaniment and not the primary abnormality. Myxedema is the most frequent of the diseases characterized by low metabolic rates. A discussion of its relation to weight will be found on pages 1058 to 1073.

These and many other studies lend overwhelming support to the statement that obesity is not caused by lessened expenditure of energy in the basal state. In fact, an obese person produces more heat than a normal person of corresponding age, height and sex. While both will

produce the same number of calories per square meter of body surface per unit of time, the obese person has a larger surface, and therefore the total heat produced by the obese person in the basal state is greater actually than the total basal heat produced by the normal person.

Strang and Evans<sup>6</sup> made careful measurements of the basal metabolic rates of 5 obese women, and the average values are compared in table 9 with the predictions for a normal woman of the same average age.

In order to emphasize the large expenditure of energy of an obese person in the basal state the authors gave the following hypothetical example: An obese woman aged 49, 5 feet (152 cm.) tall, weighs 294 (133 Kg.) pounds. Her surface area accordingly will be 2.2 square meters. Her heat production will be 77 calories per hour. In order to produce the same amount of heat in the basal state a normal man of the same age would have to be 6 feet 1 inch (185 cm.) tall.

*Specific Dynamic Effect.*—If the heat production of a person who has been without food for twenty hours and who has been reclining

TABLE 9.—*Total Basal Heat Production (Calories) of Five Obese Women Compared With Ideal Values*

	Weight, Lb.	Surface Area, Sq. M.	Calories/Sq. M./Hr.	Total No. of Calories/Hr.
Ideal.....	129	1.59	36.5	58
Observed.....	238	2.06	35.5	73

quietly and comfortably for a half hour (basal state) is carefully measured and he is then fed, he will shortly produce more heat per unit of time than he did in the fasting state. This response is not caused by digestion or absorption, since it is equally great after the intravenous injection of dextrose or some of the amino acids that result from the digestion of protein. The extra heat amounts to 200 to 300 calories in the ensuing twenty-four hours. If some metabolic fault prevented or greatly lessened this specific response to food, the person so afflicted would gain weight, provided he continued to partake of the same amount and the same kind of food and provided he did not increase his activity. His appetite might, however, direct him to eat less, since he needed less, and in that case his weight would not increase. Several students, without making any allowance for the second alternative, have attributed obesity to lessened specific dynamic effect of food.

Many attempts have been made to show that the caloric response to food is controlled by the hypophysis. Thus Plaut<sup>7</sup> stated, as a result of her studies, that a normal basal metabolic rate, coupled with a

6. Strang, J. M., and Evans, F. A.: J. Clin. Investigation 6:277, 1928.

7. Plaut, R.: Deutsches Arch. f. klin. Med. 139:285, 1922.

lowered specific dynamic response to protein, is characteristic of disease of the hypophysis. Using these criteria, she expressed the belief that she<sup>8</sup> was able to show that in certain cases obesity was caused by hypofunction of the pituitary. Kestner, Knipping and Liebesny subsequently published many determinations that seemed to confirm her work. The technic employed by these investigators has been criticized by a number of workers. Dürr,<sup>9</sup> for example, pointed out that a normal person exhibited no response to food in three hours and a response of only 18 per cent in five hours. Lauter<sup>10</sup> in careful studies found that the specific dynamic response of normal subjects varies so widely that only its total absence is of diagnostic significance. Gaebler,<sup>11</sup> working in Lusk's laboratory, found that dogs from which the hypophysis had been removed responded normally to a standard protein meal.

Because of the disagreement Johnston<sup>12</sup> reinvestigated this question. She restricted her studies to patients in whom destructive diseases of the pituitary were demonstrated, usually by operation or at autopsy. She obtained large responses in all cases (18 to 28 per cent), and pointed out that it was not possible to secure uniform results in human beings. She found it impossible to obtain a consistent response to sucrose or aminoacetic acid in a normal subject maintained on a constant diet. This again emphasized the caution with which small responses must be interpreted.

Later work suggests that the liver is responsible for the increased heat liberated during the metabolism of protein. Bollman and Magath<sup>13</sup> showed that deaminization took place in the liver, and later, Wilhelmj and Mann<sup>14</sup> found that administration of amino acids to hepatectomized dogs did not increase the heat production. Finally, Dock,<sup>15</sup> by excluding various portions of the bodies of rats from the circulation, found that at least 85 per cent of the specific dynamic heat was liberated in the abdominal viscera. He concluded that at least 80 per cent of the specific effect is due to the increased heat produced by the hepatic cells during protein digestion.

The relation of the specific dynamic effect to the obese state has been studied so painstakingly and comprehensively by Strang and McClugage<sup>16</sup> that their results may be accepted with great confidence. They emphasized that the base line, that is, the value of the basal metabolism, is the most important feature of the test. Earlier workers

8. Plaut, R.: *Deutsches Arch. f. klin. Med.* **142**:266, 1923.

9. Dürr, R.: *Klin. Wchnschr.* **4**:1496, 1925.

10. Lauter, S.: *Deutsches Arch. f. klin. Med.* **150**:315, 1926.

11. Gaebler, O. H.: *J. Biol. Chem.* **81**:41, 1929.

12. Johnston, M. W.: *J. Clin. Investigation* **11**:437, 1932.

13. Bollman, J. L., and Magath, T. B.: *Am. J. Physiol.* **78**:258, 1926.

14. Wilhelmj, C. M., and Mann, F. C.: *S. Clin. North America* **9**:829, 1929.

15. Dock, W.: *Am. J. Physiol.* **97**:117, 1931.

16. Strang, J. M., and McClugage, H. B.: *Am. J. M. Sc.* **182**:49, 1931.

have failed to train their subjects sufficiently. Strang and McClugage have repeated basal determinations until uniform results were obtained. In order to make a test acceptable they demanded that the basal calories on the test day must vary less than 2 calories from the average of measurements within fourteen days. On this basis they rejected ten of their twenty-five determinations. They pointed out the fallacy of the usual way of expressing the specific effect as a percentage of the basal calories. For example, a 10 calory increase attributable to food when the subject is producing 60 calories per hour in the basal state is an increase of 16 per cent, but the same specific increment with a basal heat production of 90 calories is an increase of only 11 per cent. Since obese persons produce more heat in the basal state than do normal persons, the same absolute response to a test diet may appear to be low in obese persons when the percentile method of comparison is used.

It is likewise misleading to express the response to a test diet in terms of surface area. Thus an increment of 10 calories due to food in a person whose surface area is 1.67 square meters gives an increase

TABLE 10.—*Specific Dynamic Effect of Food*

Type of Subject	Individual Variation in No. of Calories	Average No. of Calories
Normal.....	43 to 61	51
Obese.....	44 to 74	58
Thin.....	59 to 78	67

of 6 calories per square meter, whereas if the surface were 2.2 square meters, as is common in obese persons, the increase would be only 4.5 calories per square meter. Hence, the same absolute increase in the heat results in an apparent depression for obese subjects.

These workers emphasized the irregularity of the response to food when viewed from hour to hour and were in agreement with Benedict and Carpenter<sup>17</sup> that a true appreciation of the thermal effect of a meal is obtained by focusing the attention on the total increment.

With these considerations in mind, Strang and McClugage studied 5 normal, 5 thin and 8 obese persons. The total increment for the eight hours following the ingestion of the test meal will be found in table 10.

These studies have been described in considerable detail with the hope of convincing the reader that the acquisition of adiposity cannot be attributed to a lessened specific dynamic effect of food.

*Luxuskonsumption.*—Grafe and Graham<sup>18</sup> have maintained that in addition to the specific dynamic response, which comes to an end in

17. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Publication 216, Carnegie Institution of Washington, 1918.

18. Grafe, E., and Graham, D.: Ztschr. f. physiol. Chem. **73**:1, 1911.

twelve hours or less, the heat production of the organism throughout the twenty-four hours is influenced by the quantity of food eaten. Leaving the increases that accompany activity and the specific dynamic effect out of consideration, they expressed the belief that the intensity of the metabolism is stimulated by generous (excessive) feeding, and depressed by meager supplies of food. Such a mechanism would tend to maintain constancy of weight. Obesity would develop when the mechanism failed to respond to overeating, and leanness would be the result of abnormally great responses.

Grafe expressed the belief that he has demonstrated the existence of this mechanism by recording the heat production in the resting fasting state following various types of feeding. He denied that the basal metabolic rate of an animal is predictable from its surface area because it is significantly affected by the *calorific value of the food* previously ingested. He thus set aside the classic experiments of Rubner, Lusk, Benedict and many others, who have shown that all mammals produce heat at approximately the same rate per square meter of body surface when they are in the basal state. This generalization has been refined for the human being, for whom it has been established that slight modifications need to be made for age and sex. Many thousands of determinations have proved that the basal heat production per square meter per hour by a normal person can be predicted with great accuracy without any knowledge of what he has been eating during the preceding days.

It has also been well established that the basal oxidative rate is greatly depressed by prolonged severe underfeeding. Zuntz,<sup>19</sup> for example, showed that the decrease might amount to as much as 30 per cent of the normal value. The organism does then possess a mechanism that retards the destruction of body tissues when it has to contend with starvation. But this phenomenon seems to bear no relation to Grafe's concept that the lean organism is so because it overoxidizes an otherwise adequate supply of food or that adiposity represents underoxidation. It should be recalled that the careful studies of Boothby and Sandiford<sup>3</sup> have demonstrated that the basal metabolic rate of an obese person is normal.

Grafe and Koch<sup>20</sup> reported a study on a patient whose normal weight was 62.6 Kg. and whose height was 156 cm. Because of stenosis of the pylorus accompanied by persistent vomiting his weight had fallen to 40 Kg. In this emaciated condition he produced 30 calories per square meter per hour in the resting fasting state. The prediction for a man of his age and height and of normal weight is 39 calories per square meter. Relief of the stenosis and subsequent feeding of 100

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19. Zuntz, N.: *Biochem. Ztschr.* **55**:341, 1913.

20. Grafe, E., and Koch, R.: *Deutsches Arch. f. klin. Med.* **106**:564, 1912.

calories per kilogram brought his weight up to 60 Kg. . He then produced 40.7 calories per square meter, which was within 3 per cent of the prediction for a man of his age and height and of normal weight. This study merely confirmed Schöndorff's<sup>21</sup> earlier work that starvation depressed the basal metabolism. Grafe did not present any data to support his contention that continued superalimentation was capable of causing the oxidations to proceed at a rate greater than normal.

The reader will recall that Grafe had said that the normal organism maintains a constant weight in spite of overfeeding because the extra food stimulates the total metabolism to such an extent that the excess is oxidized, but he did not publish any data that dealt with total heat production throughout the twenty-four hours. In order to test Grafe's postulate, Wiley and Newburgh<sup>22</sup> studied the responses of a thin person by means of a method<sup>23</sup> recently developed by them for determining the total heat production for any desired length of time.

The subject was 28 years old, 6 feet (183 cm.) tall and weighed 45 pounds (20 Kg.) less than normal. For the first eighteen days he was fed a constant diet that yielded 2,922 calories daily. During this same period the twenty-four hourly heat production averaged 2,947 calories. His weight at the beginning was 57,562 Gm., and at the end it was 57,548 Gm. He was then fed a diet that yielded 4,755 calories daily. This was an increase of 1,833 calories. During the fifteen days the latter diet was taken the subject gained 4,410 Gm. (nearly 10 pounds). Heat production per twenty-four hours in the second period averaged 3,082 calories. Accordingly, he produced 135 more calories when he was ingesting about 5,000 calories than when he took about 3,000 calories, an increase of 4.5 per cent in total metabolism. The increase in the surface area that accompanied the increase in weight accounted for 68 extra calories and the additional carbohydrates and fat could be expected to increase the specific dynamic effect of the second diet by 85 calories, according to a calculation by Lusk.<sup>24</sup> Accordingly, the predicted increase in heat production during the second period without recourse to *Luxuskonsumption* is 153 calories, whereas the actual increase was only 135 calories. When the subject was partaking of the smaller diet, the fasting resting heat production was at the rate of 35.5 calories per square meter per hour. At the end of the period of overfeeding he produced 36.9 calories under the same conditions. The difference of 1.4 calories is not significant. There is, then, no evidence that either the basal or the total metabolism was stimulated by superalimentation.

21. Schöndorff, B.: Arch. f. d. ges. Physiol. **67**:430, 1912.

22. Wiley, F. H., and Newburgh, L. H.: J. Clin. Investigation **10**:733, 1931.

23. This method is described in the section dealing with the total metabolism of obese persons. See page 1045.

24. Lusk, G.: J. Nutrition **3**:519, 1931.



*Total Metabolism.*—It has repeatedly been observed that some obese patients who are receiving only minimal quantities of food fail to lose weight. Von Noorden<sup>25</sup> reported such experiences many years ago. More recently Grafe<sup>5</sup> has published several striking examples, one of which is reproduced here in part.

The patient, aged 38, was 5 feet, 4 inches (163 cm.) tall and weighed 378 pounds (171 Kg.). She became stout at 10 years of age. When she was 20 years old, she weighed 176 pounds (80 Kg.). She married at this time. Subsequently, she gave birth to 4 babies and gained weight after each delivery. When first seen by Grafe she exhibited enormous adiposity of the trunk, legs and upper arms. During the first month of treatment she lost 30 pounds (14 Kg.). Then without change in treatment the loss of weight gradually diminished, and finally, for two weeks there was no loss at all. The weight remained stationary at 341 pounds (155 Kg.). During these two weeks her diet contained 647 calories, and the basal metabolism was 2,000 calories. Grafe calculated that the daily caloric deficit was about 2,000. In addition to the restricted diet her fluid intake was limited to about 500 cc. daily. Under these circumstances the body should have lost 8.5 pounds (4 Kg.) of adipose tissue during these two weeks. Even though the patient received four injections of mersalyl solution and 3 to 8 mg of thyroxin daily, the volume of urine was small, averaging 500 cc. daily. She continued the treatment at home in a little milder form and lost 13 pounds (6 Kg.) in the next few weeks.

This capacity to resist loss of weight in spite of the most rigorous treatment has given rise to much speculation and confusion. To many physicians it has seemed useless or even cruel to continue to underfeed patients of this type, since they seemed to be doomed to hopeless adiposity.

Wiley and I have seen many examples of this phenomenon. Such paradoxical conduct might arise from some obscure metabolic abnormality that permits conservation in the utilization of energy. In that case, the total heat production would be strikingly less than normal. But no measurement of the twenty-four hour expenditure of energy had been published prior to our reports. Such patients might have been studied in a respiration chamber for one or possibly a few consecutive days. But the restricted activity and short intervals of time imposed by the chamber made that method of doubtful value for this special purpose. We accordingly investigated the feasibility of calculating the dissipation of energy for any desired length of time and without curtailment of activity from the insensible loss of weight, since Benedict and Root<sup>26</sup> had recently shown that there is a quantitative relation between the hourly insensible loss and the basal metabolism.

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25. von Noorden, C.: *Die Fettsucht*, Vienna, Alfred Hölder, 1910.

26. Benedict, F. G., and Root, H. F.: *Insensible Perspiration: Its Relation to Human Physiology and Pathology*, Arch. Int. Med. 38:1 (July) 1926.

The method <sup>27</sup> is based on the following considerations: It is well known that evaporation of water from the skin and lungs is one of the mechanisms by which the body rids itself of heat. This portion of the outgoing heat is removed at the rate of 0.58 of a large calory per gram of water vaporized. If an accurate procedure can be devised for the calculation of the weight of the water vapor and if the organism loses a fixed percentage of the heat of its metabolism by vaporization of water under a wide variety of conditions, a method will be at hand for measuring the total heat production day after day.

The direct measurement of water vapor is difficult. However, since the water vapor always accounts for the greater part or all of the insensible loss of weight, the possibility of calculating it from the latter exists.

The insensible loss of weight is easily obtained by substitution in the following equation:  $I.L. = (\text{initial body weight} + \text{ingesta}) - (\text{final body weight} + \text{urine} + \text{stool})$ , where I.L. is insensible loss of weight. And the composition of the insensible loss of weight is accurately defined in the following equation:

$$I.L. = I.W. + CO_2 - O_2$$

I.W. represents the weight of the water vapor or insensible water, and  $CO_2$  and  $O_2$  are the weights of the two respiratory gases. It must be understood that insensible water means only that water which leaves the body in the form of vapor. The water vapor is always the largest part of the insensible loss of weight and may be the whole of it, as already noted.

In order to derive the weight of the water vapor from the insensible loss of weight, one must determine the weight of carbon dioxide and oxygen for the period.

To determine whether a fixed percentage of the total heat was removed through vaporization during consecutive twenty-four hour periods by men and women who continued to lead their usual lives, we proceeded as follows (table 11, first group): The subjects were asked to adjust their clothing to avoid conscious discomfort from heat and cold and to forego strenuous exercise, such as handball. The experiments were conducted during the winter months. The subjects spent most of their waking hours in buildings heated to the usual temperature, and each of them was out of doors several times each day for a few minutes at a time. They all slept with the windows of the bedroom open. Two of the subjects were diabetic. The remainder of the group were normal young men and women busily occupied with care of patients or with work in a laboratory. The weight of each person, nude and in the fasting state, was recorded each morning at the same time on

27. Newburgh, L. H.; Johnston, M. W.; Lashmet, F. H., and Sheldon, J. M.: *J. Nutrition* **13**:203, 1937.

a balance sensitive to 1 Gm. The prescribed diet was prepared and weighed in the special diet kitchen of the hospital. The food used varied from day to day. The weights of the urine and the stool were determined each twenty-four hours.

These experiments were based on the following concepts: A well nourished adult who is following a routine of life and who is fed a fixed diet, the calorific value of which approaches his maintenance requirement, will shortly establish nitrogen balance. In addition, the glycogen store in the liver will come into balance with the carbohydrate of the diet. Thereafter, the person will oxidize carbohydrate in the amount supplied by the diet provided the time interval under consideration is not too brief. It was not expected that this principle would hold for each cycle of twenty-four hours, but that the subject would be in carbohydrate balance if each period lasted one week. Under these circumstances, change in body weight could be attributed to deposition or loss of adipose tissue, provided the observations of any subject were continued for several weeks. When the record was completed, the average daily metabolic mixture would correspond with the diet except that any change in body weight over the whole period would have to be reduced to a daily average and then 90 per cent of it either added to or subtracted from the dietary fat.<sup>28</sup> The calories of the diet thus corrected were taken to be the daily heat production of the subject.

Having arrived at the metabolic mixture, we could calculate the production of carbon dioxide and the absorption of oxygen. Since the insensible loss of weight had been determined for each twenty-four hours, the weight of the insensible water could be derived by means of the equation  $I.W. = I.L. - (CO_2 - O_2)$ .

When the insensible water is known, the heat removed by it is simply  $I.W. \times 0.58$ . From this value and the heat production the percentage of heat removed by the vaporization of water was calculated by means of the expression

$$\frac{I.W. \times 0.58}{\text{heat production}}$$

In order to arrive at a diet that would suit our purpose, we fed what experience led us to believe was a maintenance diet, measured the insensible loss of weight daily for at least one week, calculated the gaseous exchange for that diet, derived the insensible water and assumed that 24 per cent of the heat was removed by vaporization. The final diet was then constructed to contain the number of calories indicated by this approximation to the subject's heat production. However, in the case of the 2 diabetic subjects it was not necessary to use a circuitous method to arrive at the materials oxidized, since both had been living

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28. Since adipose tissue contains 10 per cent water and dietary fat is expressed in anhydrous terms, 90 per cent of the change in weight is used.

on carefully prescribed, weighed diets for years and had long since come into balance.

Table 11 shows the average percentage of the total heat lost through evaporation of water by each subject.

The first group of 7 adult persons, whose lives were restricted only in the few important ways just noted, showed a striking tendency to rid themselves of the same proportion of the heat of their metabolism by vaporization of water. The average value for the group was 24.4 per cent. The individual values varied from 23.8 to 25.2 per cent.

To obtain greater accuracy when the second group of subjects was studied, the nitrogen exchange was actually determined and the diets were restricted to a few foods the composition of which showed little tendency to vary.

TABLE 11.—*Average Percentage of Total Heat Lost by Evaporation of Water*

Subject No.	Period, Days	Age, Yr.	Sex	Heat Lost by Evaporation of Water, %	Comment
First Group					
1	72	56	M	23.8	Diabetic patient
2	5	30	M	24.2	Diabetic patient
3	18	28	M	24.2	Chemist
4	44	24	F	24.4	Chemist
5	35	25	M	24.1	Medical student
6	68	23	M	24.7	Graduate student
7	72	24	M	25.2	Graduate student
Second Group					
8	145	24	M	24.2	Student
9	30	18	M	24.3	Patient in bed
10	30	15	M	24.8	Patient in bed
11	30	18	M	24.8	Patient in bed
12	25	47	M	24.7	Patient in bed

The second, third and fourth subjects were youths aged 15, 18 and 19 who were convalescent from minimal tuberculosis of the lungs but who were still confined to bed. None of them had fever, and they felt well. They lost, respectively, 24.3, 24.8 and 24.8 per cent of the total heat produced by vaporization of water.

The last subject, a man 47 years of age, was in the hospital because of Ménière's disease. He had no attacks during the study. The data obtained on this patient are especially valuable, since he was being underfed and lost 1,787 Gm. in the twenty-five days of observation. The calculation was further complicated by a negative nitrogen balance of 1.36 Gm. daily. Nevertheless, the calculated percentage of heat lost by the vaporization of water was 24.7, even though the metabolic mixture was vastly different from the diet.

The average value for this second group was 24.6 per cent. Hence, the response of these subjects, all but 1 of whom remained in bed, was nearly the same as that of the first group, in which the subjects were leading active lives.

The uniformity of performance of these 12 persons indicates that man displays a strong tendency to rid himself, by vaporization of water, of one fourth of the heat being produced within his body, provided he is comfortable in regard to his environment. These studies also show that this tendency is maintained even when there are large differences in the total amount of heat being removed (2,200 calories to 3,600 calories).

However, since I have thus far been dealing with averages of performances these data give one no information about the extent of the day to day variation in the percentage of heat removed by vaporization of water. In order to obtain information about this question, we made use of a large respiration chamber. It was merely necessary to add to its equipment a balance capable of weighing a human being to 1 Gm.

In addition to obtaining the insensible loss of weight, we determined the production of carbon dioxide, the absorption of oxygen and the urinary excretion of nitrogen. This permitted us to calculate the weight of the water vapor by means of the equation  $I. W. = I. L. - (CO_2 - O_2)$  and the heat lost by vaporization of water ( $I. W. \times 0.58$ ).

From the carbon dioxide, oxygen and urinary nitrogen we calculated the heat production by the standard procedure.

Next we compared the heat production determined by indirect calorimetry with the value derived from the insensible loss of weight. To make the latter calculation the composition of the metabolic mixture needed to be ascertained. The urinary nitrogen was used as a measure of the protein. It was assumed that the carbohydrate oxidized equaled the carbohydrate of the diet. The fat of the metabolic mixture was calculated by means of an equation suggested by Lavietes.<sup>29</sup> Its derivation follows:

$$I. L. = I. W. + CO_2 - O_2$$

$$I. W. \times 0.58 \times \frac{100}{25} = \text{Calories}^{31}$$

$$0.58 \times \frac{100}{25} = 2.32$$

$$I. W. = \frac{\text{Calories}}{2.32}$$

$$\text{Calories} = 4.1 C + 26.5 N + 9.3 F$$

C represents carbohydrate; N, urinary nitrogen, and F, fat.

$$(CO_2 - O_2) = 0.41 C + 0.84 N - 0.08 F$$

$$I. L. = \frac{4.1 C + 26.5 N + 9.3 F}{2.32} + 0.41 C + 0.84 N - 0.08 F$$

$$I. L. = 1.77 C + 11.42 N + 4.009 F + 0.41 C + 0.84 N - 0.08 F$$

$$I. L. = 2.18 C + 12.26 N + 3.93 F$$

$$F = I. L. - \frac{(2.18 C + 12.26 N)}{3.93}$$

29. Lavietes, P. H.: *J. Clin. Investigation* **14**:57, 1935.

30. It is assumed that 25 per cent of the heat produced is lost by vaporization of water.

31. "Calories" indicate total heat production for the period.

The heat produced by the oxidation of protein, carbohydrate and fat was determined by multiplying them by their calorific values. The total heat is the sum of these three values.

We performed 39 experiments each lasting twenty-four hours, on 9 young men and women. Each subject was studied two or more times. One of them was in the third trimester of normal pregnancy. The remainder were presumably healthy persons leading active lives.

The variation in the heat lost by vaporization of water during single twenty-four hour periods was from 21.2 to 27.7 per cent. The average value was 25.1 per cent.

When the mean values of the twenty-four hour periods for each of the 9 subjects are examined, it is found that they all fall within the limits of 24.0 and 25.8 per cent. The close agreement of the average performances of the 9 subjects emphasizes the desirability of using the mean of several twenty-four hour periods whenever heat production is calculated from insensible loss of weight.

These experiments have demonstrated that the calculation of heat from insensible loss may be satisfactorily carried out on persons who continue to lead their customary lives provided they do not indulge in strenuous exercise or heavy manual labor. The advantage of measuring heat in this way is that it permits one to obtain a continuous record for as many consecutive days as is desired.

By means of this method we have recorded the heat production of a number of obese persons consecutively for several weeks and sometimes even for months. We have included subjects with various types of obesity described in the literature; that is (1) a person physically normal except for obesity who frankly admitted years of gluttony, (2) a feeble-minded girl with a low basal metabolic rate, (3) a girl with disease of the pituitary and a basal metabolic rate 30 per cent below normal; (4) a middle-aged woman whose weight had reached 295 pounds (134 Kg.) after an operation on the hypophysis eight years earlier; (5) a young woman suffering from so-called "Dercum's disease"; (6) a middle-aged woman 5 feet 2 inches (157 cm.) tall whose weight had reached 420 pounds (191 Kg.) (menopausal obesity). In no case did we find anything unusual about the total metabolism. These patients certainly did not exhibit any capacity to live at a lesser expenditure of calories than normal persons. In fact, just the opposite was true for the patients who were active. The total expenditure was large and indicated that they produced considerably more heat than persons of the same height, age and sex whose weight was normal. Our data are entirely in accord with those of Lauter,<sup>32</sup> who found that an obese subject requires more energy to perform a given piece of work than does a normal control.

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32. Lauter, S.: *Klin. Wchnschr.* 5:1695, 1926.



yielded by oxidation of body fat, and the value thus obtained was divided by 9 to give grams of fat. Knowing the grams of pure protein and fat oxidized, we needed to convert these materials to the conditions in which they existed in the body in order to arrive at the total weight of the tissues destroyed. Protein in the living organism is associated with three times its weight of water and fat with one-tenth its weight. When the protein and fat are oxidized, this water is released and excreted. The weight of the tissues destroyed is accordingly the sum of the weights of the hydrated protein and fat. This weight may be subtracted from the weight of the subject at the beginning of the experiment and indicates what he must have weighed on any day if nothing else had intervened to disturb these simple relations. This hypothetical weight is represented in the diagram by the broken line and indicates that about 150 Gm. of body tissue were destroyed daily. The solid line is the actual day to day weight of the patient. In spite of the underfeeding, the patient weighed approximately as much on the morning of the tenth day as she did on the

TABLE 12.—*Water Balance*

Water Available	Water Excreted
In food	In urine
In drink	In stool
By oxidation	Insensibly
From integral combination with tissues (preformed water)	

first. In fact, she actually gained weight the first and the second day. This capacity to resist loss of weight, even though body tissues are certainly being oxidized and the end products excreted, may last for two weeks or longer. But whatever the duration, it always gives way to a subsequent rapid loss of weight greatly in excess of the weight of the tissue destroyed. In the diagram it will be seen that this patient lost as much weight in three days (tenth, eleventh and twelfth) as she was expected to lose in twelve days because of destruction of body tissue.

It seemed to us, *a priori*, that this phenomenon might be caused by a retention of water subsequently followed by excretion of the excess. Accordingly, we undertook a study of the water balance.<sup>33</sup>

Table 12 shows the various items that go to make up such a balance.

The moisture content of the food, the urine and the stools and the weight of water drunk are determined by standard laboratory methods. The weight of the insensible water is calculated from the insensible loss of weight, as previously described (page 1046). The water of oxidation is that water which arises from the oxidation of the metabolic mixture. The method for calculating the latter from the insensible loss of weight

33. Wiley, F. H., and Newburgh, L. H.: *J. Clin. Investigation* **10**:723, 1931.



and the excretory nitrogen has already been described. When it is known how much carbohydrate, protein and fat have been metabolized, the water produced by this process is calculated by multiplying by the factors 0.6, 0.4 and 1.07, respectively. The preformed water is that water which forms an integral part of living tissue. When body tissue is oxidized, its water is released and is added to the mobile water of the body, just as if it had entered through the digestive tract. When the data are collected from subjects who are being underfed, the body stores of carbohydrate will be so depleted after a few days that no more of it is available to make up the caloric deficit and thereafter it must be derived entirely from protein and fat. The method of calculating the number of grams of body protein and fat destroyed has already been described (page 1050).

In order to control our work we first studied the water relations in a normal subject while he was being underfed. For the sake of uniformity

TABLE 13.—*Concealment of Destruction of Tissue by Retention of Water*

Day of Experiment	Change in Weight of Subject, Gm.	Weight of Body Tissue Destroyed, Gm.	Water Balance, Gm.
1.....	+285	90	+369
2.....	-225	90	-105
3.....	+ 65	90	+149
4.....	-125	90	- 41
5.....	+115	90	+198
Totals.....	+115	450	+570

he remained in bed except when he took a few steps to the scale or the commode. To minimize error we restricted his diet to milk, sugar and water. He received 63 Gm. of protein, 26 Gm. of fat and 148 Gm. of carbohydrate, yielding 1,078 calories. He produced 1,688 calories daily, derived from 69 Gm. of protein, 91 Gm. of fat and 148 Gm. of carbohydrate (averages for each twenty-four hours). Consequently, he destroyed 6 Gm. of body protein and 65 Gm. of body fat each twenty-four hours. The combined weight of these two substances in their hydrated living state is 95 Gm.

It was soon noticed that this man, even though normal, failed to lose weight smoothly. Like obese persons, for several consecutive days he would lose no weight or he might even gain weight. Then his weight would suddenly decline at a rapid rate far in excess of 95 Gm. daily.

Table 13 shows the water exchange for five consecutive days when the subject weighed 115 Gm. more at the end than he did at the beginning, even though he had destroyed 475 Gm. of body tissue. It is quite clear that the failure of the body weight to keep pace with the loss of tissue is attributable to the retention of water.

Since these events took place in a normal subject, they are deprived of all specificity for obese subjects. The excessive retention of water is seen to be merely a by-product of undernutrition. It in no way indicates that the metabolism of obese persons is abnormal.

In order to leave no doubt that the failure of obese persons to lose weight is explained by retention of water, the following case is cited:

The patient was a girl aged 14 who had always been taller and fatter than the girls of her age. Her progress in school had been slow, and she had repeated many of her grades. She freely admitted overeating and said that she much

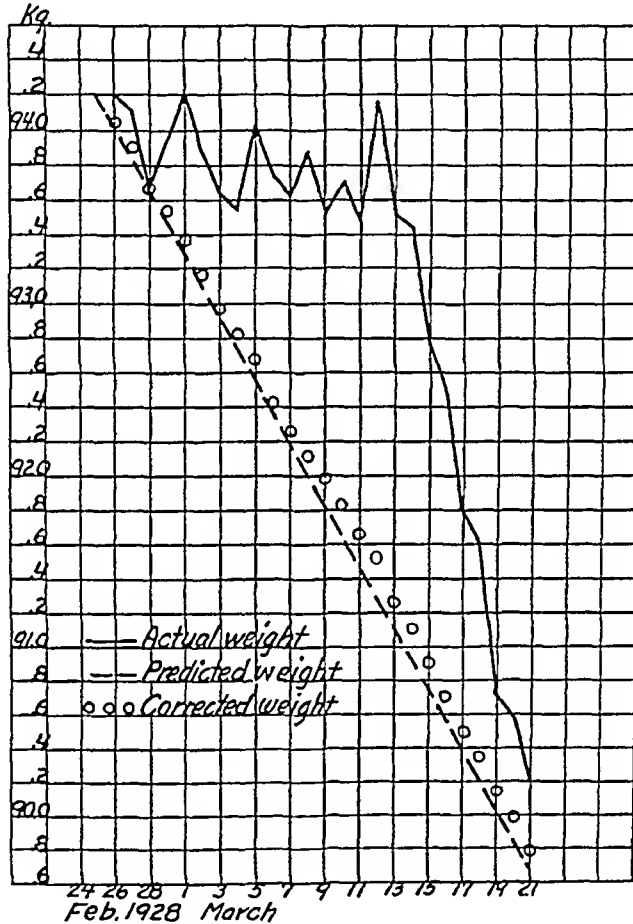


Fig. 2.—A response similar to that portrayed in figure 1. The circles represent the body weight corrected for water retention. The retention of 2,900 grams of water in sixteen days explains the failure to lose weight, since 2,900 grams of body tissue was destroyed during the same period.

preferred sitting quietly without occupation. Menstruation had begun when she was 10 years old and had been regular. She was 6 feet 1 inch (185 cm.) tall and weighed 244 pounds (111 Kg.). There was a luxuriant growth of axillary and pubic hair, and the breasts were large. Her tongue was exceptionally thick and broad. This girl was selected for study because she was obviously an abnormal type. Nevertheless, it will be seen that her failure to lose weight was attributable to retention of water, which is a normal response to underfeeding. The diet consisted of 65 Gm. of protein, 40 Gm. of fat and 74 Gm. of carbohydrate. It contained 914 calories. She produced 2,137 calories daily by metabolizing 73 Gm.

of protein, 172 Gm. of fat and 74 Gm. of carbohydrate. Therefore, the daily destruction of body tissue amounted to 181 Gm. Figure 2 shows her response to the underfeeding for twenty consecutive days. It will be noted that she weighed as much on the sixteenth day as she did at the start. Then a marked diuresis set in without any other change in the conditions of which my associates and I were aware. The diuresis continued for the next nine days of the study, by which time she had lost an amount of weight that approximately equaled the weight of the body tissue destroyed during the twenty-four days. The solid line in figure 2 indicates the actual weight each morning. The broken line states what she would have weighed in response to the destruction of body tissue, if the water balance had not been disturbed. The position of the circles was calculated by subtracting the weight of the extra water in her body from the actual weight. They show that her ability to resist loss of weight for more than two weeks was caused by progressive addition of water, which finally amounted to more than 6 pounds (3 Kg.).

The number of such studies that can be undertaken is limited, but whenever we have carried them through we have been rewarded by the demonstration that the failure of patients to lose weight when they were being underfed was always explained by retention of water.

*Increased Absorption of Food.*—After it had been generally accepted that obese persons produce more heat than normal controls, the possibility still remained that if the digestion and absorption of food by the obese persons was sufficiently more efficient than that by normal people, the former could succeed in gaining weight without overeating. Nenenschwander-Lemmer<sup>34</sup> has investigated this possibility. He compared the combustible materials in the feces with those in the diet. In a patient 5 feet 4 inches (163 cm.) tall who weighed 231 pounds (105 Kg.) he found 4.96 per cent of the nitrogen and 14.9 per cent of the fat of the diet in the stool. A control of the same height who weighed 125 pounds (57 Kg.) lost 5.49 per cent of the dietary nitrogen and 11.7 per cent of the fat in the stool. The residual calories in the feces of a group of obese persons were 5.47 per twenty-four hours, as compared with 5.41 in persons of normal weight. The utilization of the dietary calories, nitrogen and fat by the obese persons was 87, 84 and 83 per cent respectively. For the controls, the corresponding values were 88, 86 and 89 per cent. Obesity is not caused by an economy of food.

*"Lipophilia."*—Von Bergmann suggested that adiposity is caused by a hereditary constitutional trait of the adipose cells that enables them to accumulate excessive amounts of fat. He has compared obesity to growth. Just as a youth grows, even though his activity consumes great quantities of food, so some tissues accumulate fat, even though the diet might be insufficient to meet the needs of other organs. Hetenyi<sup>35</sup> carried this idea one step further by postulating that fat once deposited in the depots

34. Nenenschwander-Lemmer, N.: Ztschr. f. d. ges. exper. Med. **99**:395, 1936.

35. Hetenyi, G.: Deutsches Arch. f. klin. Med. **179**:134, 1936.

of an obese person is prevented from leaving them and so cannot be used as fuel. Increased appetite is the natural response.

To support this contention, he compared the levels of the blood fats in obese persons with those of normal persons when the usual food was taken and again after eight days of restricted diet. The data appear in table 14.

I interpret these data as evidence against Hetenyi's hypothesis. Since obese persons have more fat in the blood when food is unrestricted, they must be either storing less or mobilizing more of it than normal persons. The lowering of the blood fat level in obese persons by underfeeding is accepted by Hetenyi as evidence that they have difficulty in releasing fat from the depots in response to the increased call for energy, but it might just as well mean that fat which is being mobilized at a normal rate is being oxidized more rapidly.

Later studies dealt with blood fat curves after feeding 200 cc. of cream. The average increase in the controls amounted to 84 per cent

TABLE 14.—*Blood Levels of Fats*

Condition of Subjects	Usual Diet		Diet Planned to Insure Undernutrition	
	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.
Obese.....	544 to 1,117	890	446 to 802	630
Normal.....	371 to 1,005	591	414 to 997	607

of the fasting values as compared with an increase of only 17 per cent in the obese subjects. The individual responses, however, varied from zero to 157 per cent, and such a wide variation throws considerable doubt on the value of the averages. The lower levels in the obese subjects are offered by Hetenyi as evidence of increased avidity for fat by the depots, but since the greater metabolism of obese persons demands more fuel, why do not the lower levels of fat indicate accelerated oxidation of it?

If it were true that the adipose tissue cells of obese persons resist mobilization of fat in undernutrition, then such persons would not lose weight, or if they did, the loss would represent the destruction of body protein. But the following studies show that obese persons are less likely to go into negative nitrogen balance when underfed than are normal subjects. Jansen<sup>36</sup> placed 15 medical students whose average weight was 62 Kg. on a diet yielding 1,600 calories and 61 Gm. of protein daily for several weeks. Their average loss of nitrogen was 2 Gm. daily. Benedict's<sup>36a</sup> 12 normal subjects receiving 1,534 calories and 51 Gm. of protein lost 65 Gm. of nitrogen from the body in three weeks. On the other

36. Jansen, W. H.: *Deutsches Arch. f. klin. Med.* **124**:1, 1917.

36a. Benedict, cited by Lusk, G.: *Physiol. Rev.* **1**:523, 1921.

hand, Keeton and Dickson<sup>37</sup> showed that most obese persons on a diet yielding 1,375 calories and 90 Gm. of protein maintained nitrogen balance, and Strang, McClugage and Evans<sup>38</sup> found that obese persons receiving only 440 calories and about 1 Gm. of protein per kilogram of ideal body weight do not lose body protein.

With these things in mind, my colleague, Malcolm Block, has reinvestigated the response to underfeeding. After determining the total blood lipids during a preliminary period when the diet was unrestricted, he placed 3 normal young women and 3 obese young women on a series of diets. The first diets were arranged to yield approximately 80 per cent of the energy of the basal heat production for twenty-four hours. After seven days, blood lipids were determined again and the diets were

TABLE 15.—*Variation in Total Blood Lipids in Three Normal and Three Obese Young Women on Various Diets*

Diet	Blood Levels of Fats, Mg./100 Cc.	
	Normal Controls	Obese Subjects
Unrestricted.....	499	700
	523	540
	610	560
80 per cent of basal calories.....	706	808
	750	575
	710	700
60 per cent of basal calories.....	846	868
	843	700
	806	850
40 per cent of basal calories.....	703	910
	605	850
	542	610
20 per cent of basal calories.....	...	710
		910
		608

reduced to about 60 per cent of the basal heat. Seven days later, samples of blood were again withdrawn and the calories of the diets were reduced to 40 per cent of the twenty-four hourly basal heat production. At the end of this week, samples of blood were obtained and the obese patients were all placed on a diet yielding 450 calories. The blood fat readings are recorded in table 15. An examination of these values indicates that they rose and then fell both in the obese patients and in the controls, and it is not possible to detect any significant difference in the responses of the two groups to underfeeding.

In addition, Block calculated the dissipation of heat from the insensible loss of weight according to the principles described on pages 1044 to 1045.

37. Keeton, R. W., and Dickson, D.: Excretion of Nitrogen by Obese Patients on Diets Low in Calories Containing Varying Amounts of Protein, *Arch. Int. Med.* **51**:890 (June) 1933.

38. Strang, J. M.; McClugage, H. B., and Evans, F. A.: *Am. J. M. Sc.* **181**: 336, 1931.

And he estimated the caloric deficit by comparing the energy of the diet with the expenditure of energy. The differences were then converted to weight of body tissue destroyed, on the assumption that it consisted entirely of fat. The results for the 3 obese patients are found in table 16, which also records the daily intake of nitrogen and the urinary nitrogen. It will be seen that each of the patients lost almost exactly the amount of weight that she was expected to lose if the body tissue destroyed to make up the caloric deficit was solely adipose tissue. Furthermore, the comparison between the dietary and the urinary nitrogen shows the patients lost only negligible amounts of body protein.

All of these later studies show that obese persons release fat from the stores as a source of energy as readily as normal persons do. In fact, it seems likely that the obese persons do this more readily, since

TABLE 16.—*Loss of Weight and Daily Dietary Intake and Urinary Output of Nitrogen in Three Obese Subjects*

No. of Subject	Daily Loss of Weight, Gm.		Daily Nitrogen	
	Predicted	Actual	Intake in Diet, Gm.	Output in Urine, Gm.
13.....	254.6	255.4	13.81	14.34
14.....	250.7	249.2	13.81	13.35
15.....	222.8	222.8	13.66	13.75

TABLE 17.—*Respiratory Quotients after a Test Meal*

Hours after meal.....	1	2	3	4	6	8
Normal subjects.....	838	810	804	823	812	819
Obese subjects.....	746	772	752	740	761	795

they usually remain in nitrogen balance when they are underfed, whereas persons of normal weight do not.

The fasting respiratory quotients in obese persons are lower than they are in normal controls. According to the usual interpretation, this means that the former persons are oxidizing more fat. Quotients published by Strang<sup>39</sup> are enlightening. The fasting values obtained from 7 obese patients ranged from 0.698 to 0.830 and averaged 0.757. The controls under similar conditions ranged from 0.770 to 0.848 and averaged 0.783. These same persons were studied again after a test meal consisting of 40 Gm. of protein, 26 Gm. of fat and 52 Gm. of carbohydrate. Quotients were obtained repeatedly after the meal for eight hours and are presented in table 17.

Since both the quotients obtained during fasting and those obtained after the ingestion of food are lower in obese subjects, we have before

39. Strang, J.: Am. J. M. Sc. **182**:69, 1931.

us classic evidence that such persons are metabolizing more fat than the normal controls. They cannot at the same time be storing more fat or withholding more of it in the depots.

*Summary.*—These many painstaking investigations of the metabolism of obese persons have failed to disclose any abnormal process that accounts for the accumulation of the fat. On the contrary, they have demonstrated that obese persons produce more heat in the basal state, that they expend more energy to perform a measured amount of work and that their total heat production is greater than that of normal persons of similar age, height and sex under the same circumstances. Since they are unable to absorb more energy from their food, they must eat more than normal people simply to avoid loss of weight.

#### ENDOCRINE DISORDERS AND OBESITY

In an age when the vast influence of the internal secretions on bodily states is being emphasized by a host of workers, it is but natural that various endocrine glands have been accused of causing obesity.

*Thyroid.*—Those writers who believe that the endocrine etiologic basis of obesity has been established have expressed opinions that hypothyroidism is a frequent cause of adiposity. They based the diagnosis on a basal metabolic rate of — 10 to 25 per cent, with or without feelings of sluggishness, coldness and ease of fatigue. But these subjective complaints are so vague and commonplace that they are of almost negligible diagnostic import.

Before interpreting a low basal metabolic rate as a pathognomonic sign of hypothyroidism it is essential to recall some of the details of the test. In the first place, the apparatus records solely the amount of oxygen absorbed in a unit of time by the patient. To compare this value with a standard, the surface area of the patient must be calculated from his height and weight in order to obtain his absorption of oxygen per square meter of his body surface. This value is then compared with the average absorption per square meter of presumably normal persons of the same sex and age. These control subjects are assumed to have been completely relaxed during the test. But if some of them were not because they were a little apprehensive or uncomfortable, then the standards in general use are too high. And those best qualified to judge do, in fact, state that the standards are 5 per cent or even 10 per cent too high. Hence, a patient whose basal metabolic rate is reported as — 10 per cent may be merely one who is completely relaxed or who has fallen asleep. (Sleep lowers the rate 10 to 15 per cent.) Most of the investigators in this field have rates 10 per cent or more below the alleged normal for them, and they are probably merely demonstrating that their familiarity with the technic permits a degree of relaxation that was assumed to have occurred, but may not have, in the controls.

Some persons who are entirely at home in the metabolic laboratory have rates year after year that are 20 or even 25 per cent too low, according to the standards, and still they exhibit the attributes of health and have not become obese or myxedematous.

The custom of paraphrasing a low metabolic rate by the term "hypothyroidism" is not justifiable and certainly is misleading. If a physician wants to give a clinical interpretation to the phenomenon of lessened rate of absorption of oxygen, he can speak of hypometabolism without saying more than the facts justify. He will then be in the same position as when he deals with fever or leukocytosis. He will know that these abnormalities mean little by themselves but that when they are associated with certain other signs of disease, and only then, he is justified in making a diagnosis. When hypometabolism is associated with the classic features of myxedema, it is of course proper to attribute the clinical picture to hypothyroidism, but there exists no sound basis for believing that hypometabolism in the absence of a pale puffy face with stupid expression, hoarse voice, scanty coarse hair, water-logged tissues, anemia and general sluggishness is a sign of early or preclinical myxedema, for transition from a state in which the basal metabolic rate is as much as 30 per cent below standard, even if accompanied by mental and physical inadequacy, into classic myxedema has not been reported. Nor do the improvement in intellectual capacity and in the texture of hair, nails and skin; the relief of constipation, and the correction of menstrual irregularity obtained by administration of desiccated thyroid establish that the symptoms were caused by hypothyroidism. It must be remembered that the thyroid hormone stimulates the metabolism of all the cells. Their augmented activity may well correct symptoms that were caused by sluggish function for any reason.<sup>40</sup>

It seems much more likely that the fatigue of which many obese persons complain may be an actual indication that their muscles and other

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40. The material dealing with the interpretation of basal metabolic rate was submitted to the scrutiny of Dr. J. H. Means, who for many years has directed the Thyroid Clinic of the Massachusetts General Hospital. He replied, "I agree with all you say and would like to add my conviction that the functional activity of the thyroid gland can be gaged unequivocally by determining blood levels of iodine. Riggs and Mann, Curtis and others have devised methods which permit the accurate measurement of the concentration of organic iodine in the blood, that is to say the fraction of the iodine which constitutes an integral part of the thyroid hormone, and it has been shown by these investigators that whereas values in normal persons are 4 to 8 micrograms per hundred cubic centimeters, in patients with myxedema they are only 1 to 4 micrograms per hundred cubic centimeters.

"Thus when it is desired to establish a relation between hypothyroidism and obesity, it would be well for investigators to publish readings of the organic iodine in the blood of suitable patients as well as basal metabolic rates."



organs are becoming exhausted by overwork. Is this not the true explanation of the rapid improvement that comes with rest in bed and sharply restricted diets?

Finally, it must be emphasized that even low basal metabolic rates need not cause obesity. The organism, at least in the ideal state, obtains the amount of food that will replenish its losses. When the outgo lessens, appetite diminishes proportionately. This relation between expenditure and intake is shown beautifully by some recent experiments carried out by MacKay and Sherrill.<sup>41</sup> They introduced their data on rats with the remark,

Although it is well known that patients with myxedema are not obese as a rule, the idea persists in the clinical literature that hypothyroidism may be a cause of obesity.

In order to observe the effect of complete absence of the thyroid hormone, the gland was removed from a group of rats 170 days old. A similar group was selected for control, and all the animals were offered the same diet *ad libitum*. Three hundred and ten days later the controls weighed 457 Gm. and had gained 193 Gm. But the thyroidectomized animals gained only 178 Gm. Still more interesting was the difference in the fat content of the two groups. The bodies of the controls contained 31.1 per cent of fat, whereas only 6.4 per cent of fat remained in the bodies of the rats deprived of their thyroid glands. Since the latter animals did not appear to be less plump than their controls, it was assumed that edema fluid had been substituted for adipose tissue.

Even more enlightening is the recent statistical investigation of this general question by Plummer<sup>42</sup> on 200 patients suffering from various grades of myxedema. Sixty-one and five-tenths per cent were overweight. In 8.5 per cent the weight was more than 50 pounds (23 Kg.) above normal, but in 5.5 per cent it was more than 30 pounds (14 Kg.) below normal. The greatest excess weight corresponded to the least depression of metabolism, and those patients whose basal metabolic rates were lowest weighed the least. Thus those whose rates were not less than —28 per cent weighed 11.5 per cent too much, whereas those whose rates were less than —38 per cent weighed 14.7 per cent too little. The average excess weight for the whole group was 10.1 pounds (4.5 Kg.). During the first days of medication with thyroid there was an abrupt loss of weight that averaged 13 pounds (6 Kg.). This was brought about by elimination of fluid, since most of the patients were definitely edematous prior to treatment. Now the group weight had become 2.9 pounds (1.3 Kg.) less than normal. The excessive weight so commonly attributed to superabundance of adipose tissue is more

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41. MacKay, E. M., and Sherrill, J. W.: *Endocrinology* **28**:518, 1941.

42. Plummer, W. A.: *Tr. Am. A. Study Goiter*, 1940, p. 88.

properly interpreted as evidence of abnormal accumulation of water. In fact, judging by MacKay's rats, athyrea causes wasting of adipose tissue.

*Pituitary.*—Fröhlich's<sup>43</sup> report in 1901 of a case of tumor of the hypophysis without acromegaly seems to have originated in belief that hypopituitarism is a common cause of obesity, especially among children. He described a boy 14 years old who weighed 54 Kg. For two years he had been suffering from attacks of vomiting and headache. The left eye had become blind. The mother stated that the boy's weight had begun to increase rapidly a few months earlier. The examination revealed atrophy of the left optic nerve and right temporal hemianopsia, evenly distributed adiposity, enlargement of breasts, absence of axillary hair, pubic region suggestive of feminine type and dryness and local thickenings of skin. Fröhlich concluded that the rapidly developing obesity should be accepted as a sign of hypophysial tumor. The author cited a number of cases of similar condition proved at autopsy, but he also pointed out that poor nutrition was not uncommon in other cases of proved hypophysial tumor. Certainly there is nothing in this original report to indicate that the obesity was anything more than incidental, especially since the author himself stated that emaciation is commonly encountered in cases of hypophysial tumor.

Because of his preeminence as a neurologic surgeon the conviction arrived at by Cushing based on many careful clinical and experimental studies was accepted for a time as established fact. In 1912 he<sup>44</sup> wrote: A number of animals [dogs] in our first series, having recovered after partial extirpation of the hypophysis, were observed to grow very fat. In the second series similar results were noted. The fat proved to be widely distributed. It was not tender and no lipomata were observed.

Speaking of the clinical features of hypopituitarism in human beings, he stated:

The acquisition of an excessive subcutaneous deposit of fat is one of the notable features and often so dominates the picture as to lead to its inclusion under the following titles: *adiposis dolorosa* (Dercum's Disease), *adiposis universalis*, *dystrophia adiposo-genitalis* (Fröhlich's Disease), *adiposis cerebialis*. Undoubtedly a number of cases called *adiposis dolorosa* must be due to hypophyseal deficiency. A pituitary glioma was found by Burr in 1900 in a typical case. McCarthy found an adenocarcinoma of the pituitary in one of Dercum's cases. Lyon found an aneurism pressing upon the hypophysis.

However, in other supposed examples of Dercum's disease no changes were found. Cushing saw a woman whom he believed to be suffering from Dercum's disease. She weighed over 300 pounds (136 Kg.), but he could not locate any lesion in the pituitary.

43. Fröhlich, A.: *Wien. klin. Wchnschr.* **15**:883, 1901.

44. Cushing, H.: *The Pituitary Body and Its Disorders*, Philadelphia, J. B. Lippincott Company, 1912.

Somewhat later Cushing delineated the syndrome that goes by his name and attributed it to adenoma of the basophilic cells in the anterior hypophysis. Patients with this syndrome often exhibit a disproportion between the trunk and the extremities because of the increased girth of the chest and abdomen. Cushing attributed the enlargement of the trunk to excessive deposits of fat and reasoned that a localized adiposity could not arise from overeating but must be a direct outcome of the disease of the pituitary.

Cushing is but one of many writers who have suggested or even asserted that the obesity associated with dyspituitarism results from some unusual metabolic disturbance which in a mysterious way causes an increased synthesis and deposition of fat. Kraus has even reasoned that

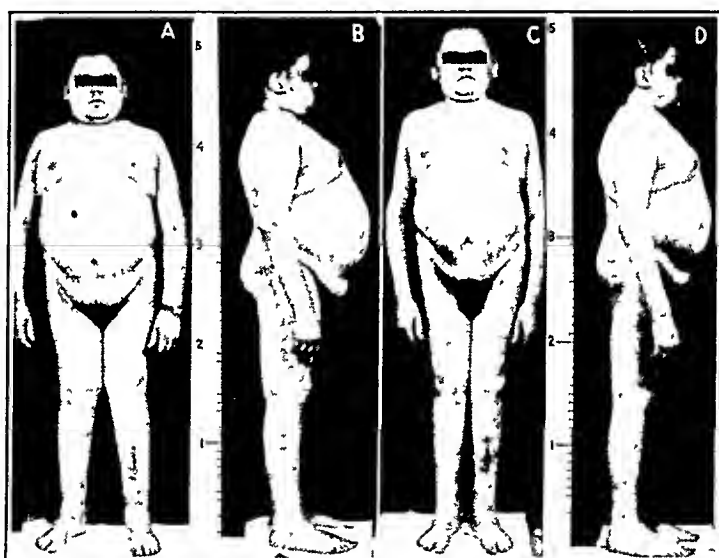


Fig. 3.—A patient with Cushing's syndrome. *A* and *B*, note the appearance of extreme obesity with an excess weight of only 50 pounds (23 Kg.). *C* and *D*, the same patient after reduction of the weight to normal. Nevertheless, the semblance of obesity persists.

a disturbance in fat metabolism is the fundamental abnormality in Cushing's disease.

Three associates and I<sup>45</sup> have recently had the opportunity of studying a case of Cushing's syndrome in which subsequent postmortem examination disclosed a basophilic adenoma of the pituitary, but we arrived at a different explanation of the abnormal bodily shape. The data that deal with the patient's configuration are reproduced here

45. Freyberg, R. H.; Barker, P. S.; Newburgh, L. H., and Coller, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of Verified Case with Discussion of Differential Diagnosis and Treatment, *Arch. Int. Med.* **58**:187 (Aug.) 1936. Freyberg, R. H., and Newburgh, L. H.: Obesity and Energy Exchange in Verified Case of Pituitary Basophilism, *ibid.* **58**:229 (Aug.) 1936.

because they show that the protuberance of the thorax and the abdomen was caused by a condition totally unrelated to adiposity.

As a child, the patient enjoyed exceptionally good health. When he was 12 years old he began to gain weight rapidly. At the age of 19, when he entered the hospital, he weighed 185 pounds (84 Kg.) and was 5 feet 2 inches (157 cm.) tall. His appearance at that time is portrayed in figure 3.

As part of the study he was placed on a diet the composition of which was the same for fifty-four days. It supplied 890 calories daily.



Fig. 4.—Lateral roentgenograms of spinal columns. *A*, normal control. *B*, the patient in figure 3. Note how decalcification has caused thinning of vertebral bodies and shortening of the spine (fish vertebrae).

The heat production was calculated from the insensible loss of weight and the urinary nitrogen, as described on page 1048. From these data we predicted that he should have lost 8,376 Gm. He did lose 8,398 Gm. This remarkably good agreement indicated that the energy exchange was entirely normal and was strong evidence that he had become obese because the inflow of energy had exceeded the outflow.

The loss of 50 pounds (23 Kg.) and the return to normal weight altered little the appearance of the unusually prominent chest and

abdomen and did not reduce their size any more than that of the extremities. Hence, the disproportionate enlargement of the trunk could not have been due to obesity. A lateral roentgenogram did, however, reveal the actual reason for the deformity. The decalcification of the skeleton, a common finding in Cushing's syndrome, had so thinned the vertebrae that the spine had collapsed, with resulting kyphosis and shortening to such an extent that the ribs had been elevated anteriorly until they were horizontal. This had swung the manubrium



Fig. 5.—Lateral roentgenogram of the thorax of the patient in figures 3 and 4 *B*. The ribs are horizontal because of shortening of spine. This has forced the lower end of the sternum upward and forward, carrying the anterior half of the diaphragm with it. The marked increase in the anteroposterior dimension of the thorax is evidenced by the horizontal position of the heart.

forward and upward. The anterior abdominal wall necessarily also moved forward. A perfect explanation for the enlargement of the trunk had been found without involving obesity. In fact, scrutiny of the cases brought together by Cushing and more recently by Freyberg reveals that obesity was not prevalent. Rather were the patients disfigured by protruding abdomens, barrel chests, short necks, kyphosis and wasted musculature.

It is of further interest that the penis and scrotum of our patient were almost invisible on admission. This appearance is held to be characteristic of Fröhlich's disease (adiposogenital dystrophy). However, when the weight had been reduced, the penis and testes had assumed the usual appearance.

Two recent publications present further evidence that the abnormal bodily configuration in patients suffering from Cushing's syndrome is



Fig. 6 (Willson, Power and Kepler <sup>46</sup>).—Note the bulging abdomen in spite of emaciation. The spinal deformity in this patient caused pronounced lordosis.

not dependent on adiposity. Willson, Power and Kepler <sup>46</sup> discussed a patient who had lost 25 pounds (11 Kg.) during the four weeks before he entered the clinic, at which time he weighed 118 pounds (54 Kg.). The accompanying photograph leaves no doubt about the emaciated state of the patient. But, nevertheless, the abdomen bulges to a striking degree, and the authors spoke of the characteristic plethoric

46. Willson, D. M.; Power, M. H., and Kepler, E. J.: *J. Clin. Investigation* 19:701, 1940.

moon face. The origin of these abnormalities is explained satisfactorily by Albright without attributing them to increases in adipose tissue, as will appear shortly. Albright, Parson and Bloomberg<sup>47</sup> studied 3 women with Cushing's syndrome and emphasized the apparent girdle obesity, "which is more the result of a relaxed abdominal wall and crushed vertebrae [decalcification] than of actual fat." Two of the women each weighed 118 pounds (54 Kg.). Certainly they were not



Fig. 7 (Albright, Parson and Bloomberg<sup>47</sup>).—Apparent girdle obesity caused by muscular atrophy.

obese. Nevertheless, the photograph of one of them does give the appearance of the so-called "girdle obesity." Albright and associates pointed out that there is a striking destruction of body protein in these patients, as evidenced by the continued negative nitrogen balance. Under such circumstances, a great wastage of the musculature takes place and the abdominal muscles are no longer able to resist the intra-abdominal pressure.

47. Albright, F.; Parson, W., and Bloomberg, E.: *J. Clin. Endocrinol.* **1**: 375, 1941.

During the early years of this century, other investigators in addition to Cushing endeavored to elucidate the functions of the pituitary by observing the effects of its removal. Opinion was divided. Like Cushing, several other investigators expressed the belief that they had demonstrated that hypophysectomy caused obesity. But Bailey and Bremer, as well as Camus and Roussy, were in doubt, since they found that injury of the brain adjacent to the pituitary was also capable of producing excessive depositions of fat. Finally, it was conclusively demonstrated by Philip Smith,<sup>48</sup> working with rats, that the removal of the hypophysis from these animals did not cause obesity. However, when the hypothalamus was injured by injection of chromic acid, obesity developed regularly after the operation. Smith explained the occurrence of obesity in the dog and its absence in the rat by pointing out that the hypophysis in the dog is separated from the brain by only a gauzelike membrane which invariably ruptures during the operation, whereas in the rat the membrane is firm and resistant. In his operations on the rat, the membrane remained intact and hypophysectomy invariably produced loss of weight, atrophy of the thyroid, the adrenal cortex and the sex organs, and cachexia.

Knowledge is now sufficiently advanced to permit the recognition of hypopituitarism when sufficient skill and effort are devoted to the clinical study. The disturbances sought for are based on the recognition that the anterior lobe of the pituitary secretes hormones which control the activity of the thyroid, the adrenal cortex and the gonads, as well as the utilization of dextrose. Its ablation in young animals causes cessation of growth in addition to atrophy of the glands just mentioned. In the adult human being the disease described by Simmond and shown by him to be due to destruction of the anterior lobe of the pituitary presents the counterpart of the condition produced by experimental ablation of the hypophysis. Here also, the most prominent features are emaciation and atrophy of the thyroid, the adrenal cortex and the gonads. Even diminished function is also recognizable, since it produces clinical pictures that suggest myxedema, Addison's disease, various signs of lessened activity of the reproductive glands and hypoglycemic episodes, present in various combinations from patient to patient. Obesity is not a feature of any of these states.

It is no longer justifiable ever to attribute obesity to hypopituitarism until its presence has been firmly established by carrying out the type of study already indicated. If occasionally patients should be discovered in whom obesity and hypopituitarism are associated, it still needs to be

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48. Smith, P. E.: Relations of the Activity of the Pituitary and Thyroid Glands, in Harvey Lectures, 1929-1930, Baltimore, Williams & Wilkins Company, 1930.



established that the former was caused by the latter. To do so, the first step would be to show a high degree of correlation between the two conditions. The clinical studies in this regard, to be discussed shortly, lead to just the opposite conclusion.

*Hypothalamus.*—Ranson and his associates<sup>49</sup> placed lesions in the hypothalamus in nearly 50 monkeys, 300 cats and many guinea pigs without obtaining obesity. Subsequently, they injected chromic acid into the hypophysis in rats by a technic that they hoped would avoid the hypothalamus. Only 3 of 50 rats became fat. Hypothalamic lesions of considerable extent were found in these 3 animals. The hypophysis showed all degrees of destruction in the 47 rats in which obesity did not develop. In another series they used the Horsley-Clarke instrument, which permits accurate localization, to place lesions in the hypothalamus in 12 rats. All became markedly obese. Subsequent examination revealed large lesions in the hypothalamic area. The hypophysis was intact. These experiments have excluded lesions of the pituitary as a cause of obesity in lower animals, and they cast formidable doubt on the proposition that obesity in human beings is ever originated by destructive disease of the hypophysis. Nevertheless, they do not preclude the possibility that hyperfunction of the pituitary is capable of inducing adiposity. However, in such typical examples of hyperfunction of the pituitary tissue as acromegaly and gigantism the excessive weight is not due to overdevelopment of adipose tissue, but rather to the overdevelopment of the skeleton and organs. And it has just been pointed out that in Cushing's syndrome, another type of hyperpituitarism, obesity is not common and certainly is not a cardinal feature of the disease.

The animal experiments seem to have demonstrated that lesions of the brain in the hypothalamic area are regularly followed by development of obesity in rats. But perhaps of more importance is the failure to produce obesity in the other mammalian species in which the hypothalamus was injured. The negative results obtained by Ranson and associates on a large number of monkeys casts a good deal of doubt on the proposition that hypothalamic lesions in human beings are the actual cause of the obesity that is sometimes seen in patients afflicted with disease of that portion of the brain.

Some light on this difficult question has been shed by Eaves and Croll<sup>50</sup> and also by Greene.<sup>51</sup> The first-named authors concerned themselves with the occurrence of obesity in patients with epidemic

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49. Ranson, S. W.; Fisher, C., and Ingram, W. R.: *Endocrinology* **23**:175, 1938. Hetherington, A. W., and Ranson, S. W.: *Proc. Soc. Exper. Biol. & Med.* **41**:465, 1939.

50. Eaves, E. C., and Croll, M. M.: *Brain* **53**:56, 1930.

51. Greene, J. A.: *Ann. Int. Med.* **12**:1787, 1939.

encephalitis. They report that Grollman noted obesity in 15 per cent of 89 patients, mostly children, and that 8 per cent of Duncan's 83 patients were obese. Hall and Stern recorded a number of obese patients in their monographs on encephalitis. On the other hand, many patients were wasted. The authors examined the brain in 10 patients who died. Two were obese; 4 were cachectic, and the remaining 4 did not show any important change in weight. In summary they stated:

There is frequently some change in the pituitary but the part played by it in the production of obesity remains obscure. The hypothalamic region was more severely affected than any other region of the brain except the substantia nigra. Severe lesions of the hypothalamus do not give rise to obesity but less intense ones may.

*Statistical Inquiry.*—Greene endeavored to discover the cause of obesity in 350 cases. He found that inactivity had occurred at the time of gain in weight in 68 per cent of the cases and that a long illness had necessitated the inactivity in 64 per cent of them. He also studied the records of 87 cases of chronic encephalitis, 18 cases of myxedema and 18 cases of tumor of the pituitary. Table 18 shows the results.

Normal weight was the commonest condition in encephalitis, and loss of weight occurred five times as often as gain. When obesity did exist, it had usually preceded the disease. These statistics throw grave doubt on the role of hypothalamic lesions as a specific etiologic factor in obesity in human beings.

Overweight was more frequent in the group of tumors of the pituitary, but the adiposity usually antedated the disease, and loss of weight occurred oftener than gain of it. Again there is nothing in any case to indicate that the nutritional state bore any specific relation to the disease of the pituitary. Even in myxedema obesity was noted in only half the cases, and it had usually existed before the onset of the disease. Weight was lost in more cases than it was gained.

The inactivity enforced by these chronic illnesses associated with good appetite seemed to be the actual cause of the adiposity when it did occur.

*Juvenile Obesity.*—Many obese children are assumed to be suffering from hypopituitarism (Frölich's syndrome) or hypothyroidism, even though one searches in vain for sufficient facts to support the contention. Bruch's<sup>51a</sup> dispassionate study of these questions is therefore welcome. Her material consisted of 102 patients, equally divided among girls and boys, 2 to 13 years old, in whom obesity was the outstanding clinical condition. Weight at birth was normal; normal development

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51a. Bruch, H.: Obesity in Childhood: I. Physical Growth and Development in Obese Children, *Am. J. Dis. Child.* 58:457 (Sept.) 1939.

was the rule, and puberty was attained at normal age or earlier. Obese children are taller than normal ones, and skeletal growth, as determined by roentgen rays, is accelerated. Normal girls who menstruate early are taller and heavier than those in whom the onset is later. Bruch concluded:

The condition of the obese children manifests an exaggeration of a developmental trend observed in normal children; the difference is only quantitative. . . .

She found that the oxygen consumption of an obese child is greater than that of a normal child of the same age and height. The serum cholesterol, which is increased in myxedema, was normal in 72 obese children. Bruch was satisfied that

. . . the course of growth and development of obese children . . . cannot be brought into agreement with the well defined picture of hypothyroidism [or]

TABLE 18.—*Weight in Relation to Certain Diseases*

	Chronic Encephalitis	Myxedema	Tumor of the Pituitary
Normal weight.....	52	11	7
Underweight.....	19	1	4
Overweight.....	16	6	7
Relation of Obesity to Onset			
Antedated.....	16	4	5
Postdated.....	5	3	3
Disappeared with.....	5	1	1
Change in Weight after Onset			
No change.....	16	8	6
Gain.....	6	6	5
Loss.....	33	5	7

. . . hypopituitarism. . . . It is not reasonable to explain accelerated development as resulting from hypofunction of glands the growth-promoting qualities of which are firmly established. . . .

Nevertheless, the treatment of choice and often the only therapy of the children referred to the obesity clinic continues to be administration of endocrine products, according to Bruch. When pituitary preparations have been recommended, the physician has done so because he has made a diagnosis of adiposogenital dystrophy, basing it on the presence of adiposity coupled with retarded development of the genitalia. But recent studies have made it clear that genital infantilism is far less common than is widely believed. In this connection, Bigler, Hardy and Scott<sup>52</sup> pointed out that the incidence of undescended testicle in the United States Army is 0.3 per cent, whereas at the Hospital for Ruptured and Crippled, New York, incomplete descent was diagnosed

52. Bigler, J. A.; Hardy, L. M., and Scott, H. V.: Gonadotropic Principle in Treatment of Cryptorchidism: Review of Literature, *Am. J. Dis. Child.* 55:273 (Jan.) 1938.

in 3.0 per cent of 18,000 children. This means that in 9 of every 10 children in whom the diagnosis is made, the testicles will subsequently descend spontaneously. Browne<sup>53</sup> called attention to a series of misconceptions which lead to incorrect diagnoses. He states that any position from which the testes will reach the scrotum is normal and that the belief that a testicle which can be felt in the region of the inguinal canal is in that canal is a common mistake. Gonadotropic substances will not bring down a testis that would not have descended without such treatment. Its only power is to hasten descent. Spence and Scowen<sup>54</sup> confirmed Browne's findings. Accordingly, the descent of a testicle in a fat boy after treatment with gonadotropic substances should not be accepted as evidence that he was suffering from hypopituitarism. Bruch stated that in none of her patients who had been made miserable and unhappy by a diagnosis of sexual maldevelopment was this diagnosis justified.

In a recent publication Bruch<sup>55</sup> reported the histories of 2 children in order to emphasize that the diagnosis of an endocrine cause of juvenile obesity is not supported by the known facts. But even more impressive is her convincing argument that serious harm may be done to children who receive glandular therapy unnecessarily.

When the first patient was 5½ months old, he had been examined at a pediatric clinic. No abnormalities other than poor development of the genitals had been found. When the child was 15 months old, a physician in the urologic clinic had been unable to feel either testicle, and treatment with chorionic gonadotropin (follutein) was begun. The child had continued to receive courses of this material subcutaneously until he was 6 years old. When he became a patient of the Pediatric Obesity Clinic, a division of Vanderbilt Clinic, New York, it was noted that the genitalia appeared small. Their true size however was masked by an accumulation of suprapubic fat. When this was pushed back, it was seen that the penis and scrotum were well formed. His weight had been normal when the glandular treatment was started, and it was not realized that he was gaining weight too rapidly until he was 6 years old, when he weighed 45 per cent in excess of the normal. At this time a diagnosis of "adiposogenital dystrophy" was made because of the marked accumulation of fat in the abdomen, suprapubic region and thighs and the round face and sluggish expression, together with the apparently infantile genitalia. Bruch pointed out that the development of the so-called "pituitary" type of obesity in a patient being treated intensively with gonadotropic substance is substantial evidence against the correctness of such a diagnosis.

It was now learned that the patient, who was an only child, had experienced a local swelling with pain and a general reaction consisting of rise in temperature to 102 F. accompanied by nausea after each injection. Nevertheless, he had been given three injections weekly for protracted periods. Shortly after the treatment was begun, he had become apprehensive and listless. He never was able to dress

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53. Browne, D.: *Brit. M. J.* **2**:168, 1938.

54. Spence, A. W., and Scowen, E. F.: *Lancet* **2**:983, 1938.

55. Bruch, H. J.: *J. Pediat.* **18**:36, 1941.

himself and did not care to play. On the other hand, he always enjoyed his food and ate everything his mother gave him. In retrospect, she realized that she had overfed him to compensate for his illness.

After the first visit to the Obesity Clinic he was lost track of for a year. The explanation was then forthcoming. Because of prolonged illness both of mother and of father the patient had been shifted from one relative to another. Finally, a crippled woman, who could do little for him, was put in charge of him. At the end of this year he was a changed child. He dressed and bathed without aid, did not object to being left alone, played on the street and defended himself. In spite of growing 2 inches (5 cm.) he had lost 5 pounds (2.5 Kg.).

In retrospect, it is seen that the persistency of subcutaneous medication, even though it caused unpleasant reactions, naturally led the mother to surmise that her only child was seriously abnormal. The patient's timidity and listlessness were further evidence that he was suffering from a chronic illness. She responded by attempting to compensate for his disability by protecting him in every way and by giving him the satisfaction obtainable from large and varied feedings.

The second patient, a girl, had been brought to the Pediatric Department when she was 5 years and 2 months old for treatment of asthma, from which she had suffered for six months. Her weight was normal. After one year's treatment she had had no further attacks. At that time, when her weight was still normal, moderate enlargement of the thyroid had been noted. Accordingly, she had been followed in the Thyroid Clinic for the next five years. There it was recorded that the gland was nodular and firm, but that there were no manifestations of hypothyroidism. The basal metabolic rate was  $-30$  per cent, according to the surface area standard. One week later it was  $-13$  per cent. Calculation of the rate on the basis of height and weight standards gave values of  $+5$  per cent and  $-2$  per cent, respectively. For prophylactic purposes she had been given minute amounts of thyroid and syrup of hydriodic acid U. S. P. for the next two years. During this period she had gained weight rapidly and had become markedly obese. When she was 11 years of age, the thyroid gland was considered to be normal. The basal metabolic rate at this time was  $-19$  per cent according to surface area standard,  $\pm 0$  according to height standard and  $-8$  per cent when referred to weight.

When seen for the first time in the Obesity Clinic she was  $10\frac{1}{2}$  years old and 40 per cent overweight.

The patient, an only child, had never been allowed to go out in cold or wet weather, and association with other children had been discouraged by the parents with the hope of avoiding asthmatic attacks. Up to the age of 12 she had not been allowed to take a bath alone and was still being sent to the toilet. Even though the last attack of asthma occurred when she was 6, the parents were afraid to relax the precautions devised to protect their child.

The obesity was explained by the parents and the patient as due to the "lazy gland," even though the family had been reassured repeatedly that the thyroid was normal. When a reduction diet was suggested, the mother expressed fear that it would be harmful to a child with a "lazy gland," and the patient was openly antagonistic to any treatment.

In this case as in the previous one the exaggerated anxiety and misinterpretation of the medical situation resulted in parental conduct that deprived the children of most of their normal outlets. They became self centered and considered themselves deserving objects of pity and special consideration. Under such circumstances the satisfactions derived from eating were about the only pleasures still permitted the children. It would have been strange indeed if they had not made the most of them.

My associates and I have been especially interested in the obesity of young adults that had its onset years earlier in association with an illness. Careful questioning is usually rewarded by the discovery that the mother had been instructed to prevent all physical activity on the part of her child, who had just passed through an illness which was thought to have caused heart disease. Even though activity is cautiously increased months later, the young patient continues to be trained to avoid exercise and to guard against heart strain. The mother, not realizing that the needs for food are greatly reduced in these circumstances and still under the sway of the time-honored belief that recovery will be enhanced by full feeding, spares no effort to tempt the child to eat. The young patient, suffering from self pity and egoism, accepts the food, even though he has no inherent desire for it. As time passes, conditioned reflexes become firmly developed, and the feeling of satiety does not occur until the child has overeaten in the physiologic sense.

#### HEREDITY

The interesting observations published by Danforth<sup>56</sup> proved that in at least one mammalian species there exists a gene that causes its possessor to become obese with great regularity. Yellow male mice were mated to females of various colors. Some of the descendants were yellow, others were not. Litter mates were kept in the same cage and had access to the same food. After sexual maturity had been attained, the yellow mice began to gain weight more rapidly. This was especially true for the yellow females, many of which reached a weight twice that of their mates. The excess weight was mainly due to a great and widely distributed increase in adipose tissue. Our own studies, still in a preliminary state, of this hereditary obesity of yellow mice permit the statement that the mice which become obese eat more than the others. Evidently one is dealing with a hereditary bulimia.

Before considering whether a similar gene is transmitted by human beings, it will be well to give some thought to the configuration of the body. No one questions the inheritance of bodily shape or build. Everyone is familiar with the characteristic lines of purebred dogs. One has merely to recall the contrasts between the slender, graceful, agile grey-

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56. Danforth, C. H.: *J. Heredity* **18**:153, 1927.

hound and the thick-set, ponderous English bulldog. But even though the bulldog is robust and powerful, he is not obese. However, he may be pampered into overeating and become so.

Similarly, the human being who has inherited a sthenic build is not predestined to become obese. Pains must be taken to explain to him that the two qualities are not linked—that while shape is inherited, obesity is an acquired characteristic.

Adipose tissue is much more abundant in some parts of the body than in others, and women normally possess more fat than men. Furthermore, there is commonly a large accumulation of fat around the hips and loins of women of normal weight. And since the pelvis of a woman is flatter than that of a man, she starts with two handicaps when she becomes obese. The so-called “girdle” obesity merely accentuates a normal type of feminine configuration. While it may well be true that the deposition of the excessive fat in the central regions of some women is an inherited characteristic, it is also true that there would have been no extra fat to deposit in those regions had the intake of food not been overabundant.

The prevalence of obesity in some families need not be accepted as an inherited and therefore an unavoidable trait. A more realistic explanation is the continuation of the familial tradition of the groaning board and the savory dish.

The question of whether human obesity is an inherited characteristic has been investigated extensively. Such studies are based on the proposition that identical twins are genetically identical throughout and that differences in the individuals of such a pair are due to environmental influences. Accordingly, differences in body weight are caused by environmental influences. Both Verschuer<sup>57</sup> and Newman and associates<sup>58</sup> found that weight varied more than any of the other anthropologic measurements. In fact, the average variation in weight was always twice, and mostly three times, as great as that of any of the other variables. This emphasizes the important influence of environment on weight.

Furthermore, Verschuer compared the variations among identical twins living under similar conditions with those among twins living under dissimilar conditions. Differences in weight were two and a half times as great when environment was dissimilar. On the other hand, Newman and his associates expressed the belief that they have demonstrated that environmental factors cause smaller differences between the two members of a pair of identical twins than between fraternal twins. But since the external influences themselves were so variable, it seems to me unjustifiable to use the responses to them as a basis for drawing conclusions.

57. von Verschuer, O.: *Ergebn. d. inn. Med. u. Kinderh.* **31**:35. 1927.

58. Newman, H. H.; Freeman, F. N., and Holzinger, K. J.: *Twins: A Study of Heredity and Environment*, Chicago, University of Chicago Press, 1937.

While it is freely admitted that such features as height, the sweep and contour of the body's lines and the color of eyes and of hair are transmissible characters, one hesitates to believe that the weight of a human being is determined by inheritance, because, as I have emphasized in this monograph, weight is so easily and greatly altered by environmental conditions. It may be true that a good or a poor appetite is an inherited feature and that given identical environment those persons born with the good appetite would become obese. But the environmental experiences to which a person is exposed are highly varied, and his desire for food is greatly affected by the character of his world. It will be conceded that fashion is a potent determiner of weight. Has not the urge to be slim so governed the appetite that the young women of America are underweight, and have they not succeeded in training their appetites so that they habitually do not partake of food in excess of the small amounts that will just maintain their slight bodies? Does not the big business man, who considers portliness one of the attributes of his success, acquire and maintain a generous girth by indulging in rich and sumptuous meals?

Why did a little boy whose weight had been normal, become obese, self centered and dull subsequent to an attack of scarlet fever when a physician had informed his mother that her son's heart had been damaged by the infection and that he must remain in bed for months and subsequently must be trained to avoid activity? Why did he again lose weight some years later when boys at a preparatory school laughed at his feminine appearance, and why did he go in for athletics after another physician assured him that his heart was normal? Surely these are not inherited responses.

It must be concluded that one of the reactions of the human being, so responsive to the flood of stimuli impinging on him, takes place in the sphere of appetite and that obesity is a product of his environment.

✓ *Summary.*—It is hoped that the foregoing discussion has convinced the reader that obesity is never directly produced by increased or diminished activity of an endocrine gland. In other words, no internal secretion is capable of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow.

It remains for the future to decide whether a hypothalamic disorder or other cerebral disease is capable of causing human obesity through abnormal stimulation of appetite. Whatever the answer, the simple principle will remain that obesity is invariably the result of a disproportion between the inflow and the outflow of energy. The former must always be greater than the latter; because either the intake has increased or the outgo has diminished.



The suggestion of von Bergman, so volubly defended by Bauer, that the fat cells of obese persons possess an abnormally great avidity for fat and an exaggerated capacity for retaining it finds no support in experiments designed to test its validity.

Body build is inherited; obesity is not.

#### HUNGER AND APPETITE

In the ideal state the living organism is directed by hunger to secure food in amounts sufficient to replenish the bodily materials that have been destroyed by oxidation or have been excreted. This primitive mechanism does not give rise to sensations which are primarily pleasurable. It is, so to speak, more business-like than that. With the passage of time hunger has come to be so closely associated with other feelings called appetite that the mind of man no longer distinguishes clearly between the two. Appetite, strictly speaking, is a sensation produced by happy memories. The desire for food may be the expression of real hunger, but it is more generally a response to habit or the anticipation of pleasure. It is modulated by the emotions to a striking degree. Fright, fear, sorrow, illness and displeasing sights and smells depress or even abolish it. It is stimulated by foods that give off pleasant odors, that please the eye and the palate. Happy recollections and good companionship are conducive to overeating. It may be that the long established habit of eating certain quantities of food has a more profound influence on the appetite than does the intervention of lessened physiologic needs associated with hypofunction of an endocrine gland. Most persons know the pain that must be endured when the old path is abandoned.

A number of writers have marvelled at the accuracy with which the appetite meets the bodily needs, because the weight of most healthy adults scarcely changes from year to year. It is stated in a well known textbook that a man 20 years old who weighs 75 Kg. will double his weight in another twenty years if he merely eats one butter pat (8.9 Gm. of fat) in excess of his caloric requirement every day. But the author apparently failed to take into account the enlarging surface area that accompanies increasing weight. Consider for example, a normal man who weighs 75 Kg. (165 pounds). He would be 5 feet 10 inches (178 cm.) tall, and his surface area would be 1.91 square meters. At age 20 his normal basal heat production would be 41 calories per square meter per hour. Accordingly, this hypothetical person would have a basal heat production of 1,880 calories per twenty-four hours. If he consumed 80 calories a day in excess of his maintenance requirements, the resulting gain in weight would be accompanied by an increase in the area of his surface, which would become 1.98 square meters when his

weight had reached 81 Kg. The corresponding normal basal metabolism would now be 1,956 calories per twenty-four hours, instead of 1,880 calories. The calories yielded by the extra butter fat would then merely furnish the heat of the increment in basal metabolism, and the subject would no longer store fat unless he made another addition to his diet. The solid line in figure 8 shows the lessening gain in weight correspond-

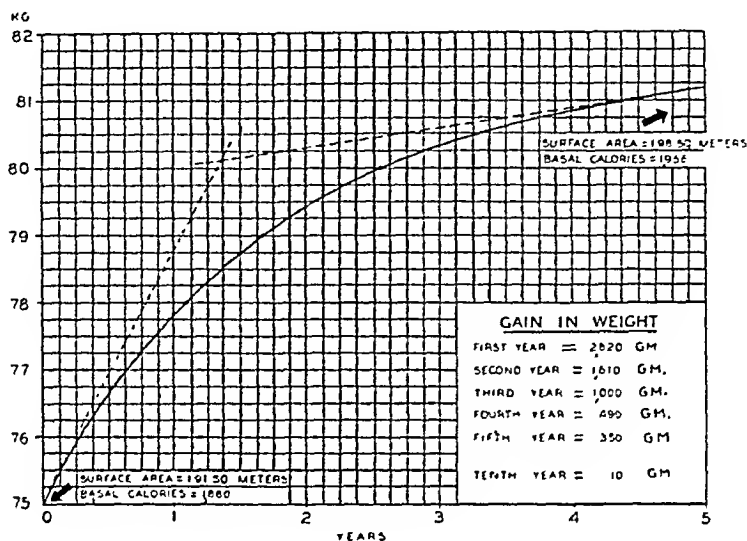


Fig. 8.—Weight plotted against time, with an initial dietary excess of 80 calories per day.

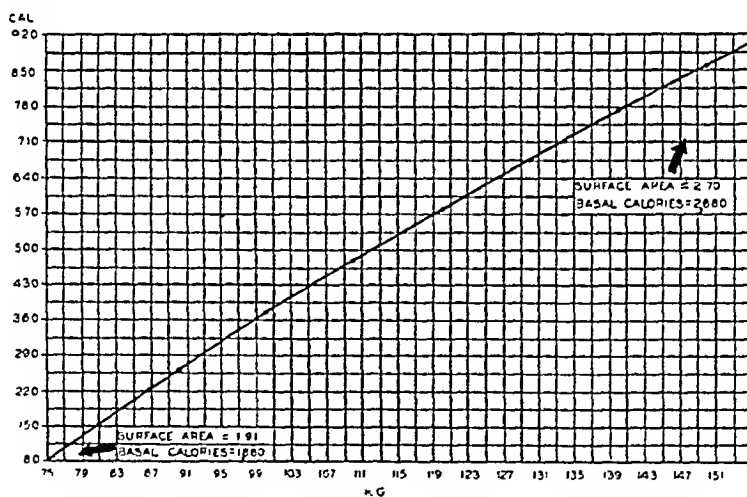


Fig. 9.—Excess calories plotted against weight.

ing to the increasing surface area. The broken lines indicate the rate at which weight would be added in the first and in the fifth year. Figure 9 shows how the diet would have to be progressively increased in order to permit the subject to continue to add to his weight at the rate at which he did so during the early weeks when the forbidden butter pat was actually furnishing 80 calories in excess of his requirement. By the time the man had doubled his weight, he would have increased his diet by 990 calories, not 80.

These calculations assume that the activity of the subject remains constant through the years and that the added weight does not lessen his efficiency.

*Inaccuracy of Appetite.*—Harrington<sup>59</sup> has been interested in the inaccuracies of the appetite. She has devised experiments that test its capacity to supply a subject with the right number of calories when he is offered different types of food. Three meals a day were served, and more food was offered than was consumed. The subjects were asked to eat as much as they desired, but they were given no information about the composition of the diets, all of which were adequate. The standard diet contained 1.5 to 2 calories per gram. A bulky diet was prepared by omitting concentrated foods and emphasizing fruits and vegetables. It contained 1 calory per gram. All subjects lost weight while taking it, because they ate only their habitual volume of food. The concentrated diet was constructed by substituting cream and butter for the milk of the standard diet and by increasing the sugar. It yielded 2.5 calories per gram. All subjects gained weight. They enjoyed this diet to the extent of eating more of it than was needed to satisfy the physiologic demands.

Harrington spoke of a patient who had had a thyroidectomy for exophthalmic goiter one year previously. Since then she had made a marked gain in weight. When she entered the hospital the second time her basal metabolic rate was 30 per cent below normal. She was kept on a diet of fixed composition and instructed to eat enough of it to satisfy her appetite. During the next eight days she took 2,450 calories a day and gained 900 Gm. Thyroid medication was then instituted. After the metabolic rate had become normal, her average intake was only 2,366 calories for eleven days, even though she lost 1,700 Gm. in these few days. Her appetite seemed to have lost contact with the fundamental requirements.

Another patient from Harrington's series is cited to emphasize how strongly appetite may be affected by the will. A girl 16 years old and 5 feet 7 inches (170 cm.) tall weighed 264 pounds (120 Kg.) when she entered the hospital. She was placed on a 1,000 calory diet and given careful instruction in its preparation. She lost 13 pounds (6 Kg.) in ten days. She returned six years later weighing 279 pounds (127 Kg.). This time she seemed to be in earnest because she had found that her size was such a handicap in securing a position. To learn whether her attitude toward food had really changed, she was offered a bulky diet containing 1 calory per gram. Each day she was served 4,000 grams of this diet, but she was given no instruction or information about the diet. For fifty-nine days her average intake was

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59. Harrington, M. M.: J. Am. Dietet. A. 6:101, 1930.

1,839 calories, and she lost 29 pounds (13 Kg.). The diet was next cut in half. Now she took 1,465 calories on the average for fifteen days. She was then discharged without instruction. During the next thirty days she lost 11 pounds (5 Kg.).

Evidently the primitive signals which notify the mind that it is time to restock the bunkers are often confused by emotional currents.

The matronly figure is not an unavoidable, although a common, sequel to the menopause. It does not mean that the secretions of the sex glands, now in abeyance, formerly had the power to restrain the growth of the adipose tissues. Rather does it indicate that the woman has reached that stage of life when she needs to strive less and finds more time for leisure. Even though she now needs much less food, she has more time in which to enjoy it and feels that she has earned the right to indulge herself. Probably she does not know or is but dimly aware that the candies she nibbles at the bridge parties which she so enjoys now that she is rested are adding their quota to her girth. Or if she is aware of the facts, she does not resist gain in weight, since the friends in whom she has the greatest confidence have assured her that nature intends her to lay on weight at this time of life. At first she still recognizes the signals that notify her that she has had enough to eat, but she deliberately ignores them because she has "toed the mark" long enough and from now on she is going to "humor herself." Gradually, the warnings become so blunted that she continues to enjoy gustatory pleasures until they are finally displaced by the discomforts attendant on ingestion of great excesses of food.

*Emotional Craving for Food.*—Other people grow fat because life has become more difficult for them, not less so. They are persons who are struggling with a problem—sexual, social or financial—for which they can find no solution. But they have discovered that they obtain temporary solace in eating. For them food acts as a balm, as alcohol does for others who find life too hard. We have seen many obese patients who either deliberately or without being aware of the situation have turned to food as a means of relieving pent-up emotions. The following case history is a good example of the development of obesity in a patient who strove to lessen the pain of overwhelming disappointment by incessant eating.

The patient was an unmarried woman aged 41, 5 feet 4½ inches (164 cm.) tall, who weighed 225 pounds (102 Kg.) when she entered the clinic. When she was 25 years of age she found herself deeply in love with a young man, but her father was firmly opposed to their marriage. During the next six months she battled with the problem whether she should obey her father, whose guidance she respected, or should disregard him. She finally decided in favor of the father. By this time she had become so disturbed emotionally that she could not bring herself to face the world. In order to avoid contacts, she refused to leave the second floor of her home for four years and remained in bed

most of the time. She gave no thought to the food that was brought to her by a servant except that she was aware of eating a great deal of sugar. The emotional instability became less marked after a time, and then she began to realize that she was causing her parents great pain and that she must once again take up the usual mode of life. At the beginning of the period of isolation she weighed 117 pounds (53 Kg.). When she emerged, her weight was 161 pounds (73 Kg.). She then went to a doctor for reduction of weight. He gave her a diet and 2 grains (0.13 Gm.) of thyroid daily. In less than a year her weight had diminished to 125 pounds (57 Kg.). Her father died suddenly shortly thereafter. At that time the family lived in a large house which they had previously been able to maintain generously, including the employment of servants. The patient now suddenly discovered that the family finances were in a precarious condition, and she decided that she must do all the work in the house. Even though there were only her mother and herself at home, she began her work at 4 o'clock in the morning and attempted to do all of the cleaning, cooking and laundering. She shortly found herself overwhelmed with fatigue, and the fear that she would be unable to continue the work caused her to attempt to gain strength by eating a great deal. Soon she disregarded the regular meal hours and ate whenever she felt exhausted. She continued to struggle on in this way for about a year, when her weight had reached 177 pounds (80 Kg.). And now she had to admit to herself that the large amount of food she had been eating had not helped her. In fact, she fatigued more easily than before and was hampered by shortness of breath. But she was chiefly disappointed because the obesity disfigured her. She tried to reduce her weight (without the aid of a physician), but she continued to gain nevertheless. When she realized that she was failing again, she became tense, restless and was harassed by insomnia. It seemed useless to make any further effort. Since she could calm herself temporarily by eating, she no longer resisted and ate whenever she felt distracted. She gained 50 pounds (23 Kg.) in less than a year. Then she concluded to make one more attempt to reduce her weight and came to the hospital for that purpose.

The examination disclosed no abnormalities other than the adiposity. She was instructed to eat all her meals in the special diet kitchen, where she received 450 calories daily. During the next four months she lost approximately 60 pounds (27 Kg.). After she adhered to the diet for a few weeks, the craving for food had disappeared and her appetite was satisfied. She was amazed.

About a month later she became emotionally upset and experienced a distaste for food. For a time she refused a good deal of the diet, but this episode lasted only a few days. Subsequently she adhered strictly to the plan and had no desire to eat more than she was offered. Accompanying the conviction that her weight would soon be normal again, a change in attitude occurred. She no longer worried and found that she was calm and philosophic.

The next case is another typical example of the use of huge quantities of food to assuage a seemingly hopeless situation. This time it was the physical and mental cruelty inflicted by a drunken husband.

The patient was 25 years of age when she entered the clinic. Her height was 5 feet 7½ inches (171 cm.) and she weighed 248 pounds (113 Kg.). She had been married six years previously to a man who was apparently a successful innkeeper. The first three years of married life were peaceful and pleasurable. Then, for no reasons evident to the patient, the husband began drinking heavily, took to gambling, neglected his business and went into debt. He became ill humored and

rough. To increase his income he converted the inn into a brothel and demanded that his wife, who was one of the waitresses, permit the male patrons to have sexual intercourse with her just as the other girls did. Her initial refusal was overcome by beating her so violently that she had to remain in bed for a week or two on numerous occasions to recover from the attacks.

She now noticed that for the first time in her life she was nervous and irritable and that she was annoyed by a gnawing sensation in her stomach. The latter discomfort was relieved by food, and she was gratified to find that large frequent meals made her better able to tolerate her lot. She now deliberately used food, wine and whisky to comfort her. It was not unusual for her to eat three large steaks a day and fill in the intervals with almost continuous munching of anything that caught her eye, and she "washed down" the solid foods with generous draughts of beer, interspersed with frequent gulps of wine and whisky. At the beginning of this period of overeating she weighed 148 pounds (67 Kg.). This was normal for her. During the next two and one-half years she gained 100 pounds (45 Kg.). She was divorced at about that time and has not gained since.

The examination disclosed a slovenly, unkempt young woman who suffered great emotional pain as she revealed her cruel experiences. She expressed great gratitude and relief when she began to feel that we intended to treat her in a dignified manner, that we understood her problem and that we were confident that we could make her a presentable young woman by reducing her weight to normal. She lost 17.1 pounds (8 Kg.) during the period of thirty-one days while she was an inpatient. She was discharged on a diet of 450 calories daily and has adhered to it without any difficulty.

*Food Habits of Obese Persons.*—Most recent writers have taken the position that obesity must be caused by a positive balance of energy. Since the expenditure of energy by obese persons is at least as great as that of normal persons, the law of conservation of energy demands an excessive inflow of calories to explain the adiposity. But it is perhaps possible that this law might be evaded by some metabolic aberration that has escaped detection. It is therefore important to study the food habits of obese persons as well as their dissipation of calories. A good deal of information about this question is available. In Lauter's<sup>10</sup> experience, patients suffering from "endocrine" forms of obesity consume amazing quantities of food exactly as do patients with obesity due to other causes. Dunlop and Murray Lyon<sup>60</sup> inquired into the dietary habits of a large group of patients. They found that an excessively large and poorly balanced diet was, among all the factors examined, the one most commonly present. Lambie<sup>61</sup> and Campbell<sup>62</sup> reported similar observations. Kisch<sup>63</sup> went further. He had 50 obese patients keep records of their food consumption. It ranged from

60. Dunlop, D. M., and Murray Lyon, R. M.: *Edinburgh M. J.* **38**:561, 1931.

61. Lambie, C. G.: *Brit. M. J.* **2**:885, 1935.

62. Campbell, W. R.: *Canad. M. A. J.* **34**:41, 1936.

63. Kisch, F.: *Ztschr. f. klin. Med.* **132**:504, 1937.

2,900 to 3,500 calories per twenty-four hours. Thirty patients who remained in bed were fed 200 calories in excess of their basal requirements. Twenty-eight of them complained of hunger. The obvious inference was that they had previously eaten much more.

Bruch<sup>64</sup> has made an exhaustive study of the food habits of 142 obese boys and girls, 2 to 13 years of age. She remarked that the tendency of the children and of their parents to minimize the food intake was encountered frequently but detailed questioning usually revealed the true picture. One mother, for example, who first answered, "Just normal, he doesn't eat much," later in the interview stated, "I know; I stuffed him like a goose." Nearly all the children had eaten excessive amounts of starchy food. She mentioned a boy of 10 who admitted six slices of bread, as sandwiches, a piece of cake, four apples and five bananas as a regular lunch, in addition to several glasses of milk. Not one child had learned to eat a mixed, well balanced diet. Vegetables and salads were the foods most frequently disliked. All children ate between meals whenever they felt like it. Bruch was convinced that the children became fat in all cases because they overate. She emphasized the close association between overeating and the lack of social maturation. Many of the children, for example, were incapable of dressing themselves. It was not unusual to learn that a child of 10 years was still being dressed and bathed by the mother and was not allowed to play with other children. This overprotection, which deprives the child of normal outlets, turns his attention to the satisfaction gained by eating. The obesity in other children dated from an upsetting experience. Often the fear that sexual development was abnormal had given rise to self pity and compensation in gluttony.

One is forced to conclude that obesity is invariably caused by eating more than the body needs, whether the patient be an adult or a child. Overeating is the expression of a habit or of a mood.

*Hypoglycemia.*—It has been suspected that the hunger caused by hypoglycemia has driven some patients to overeat and so become obese. This idea seemed to be supported by the observations of a number of investigators who reported that the appetite of emaciated patients could be stimulated by injections of insulin. However, Freyberg,<sup>65</sup> who attempted to confirm these observations, found that the whole effect was obtained through suggestion, since injections of solution of sodium chloride increased the appetite as successfully as insulin did. Further, he found that insulin had no effect on appetite unless the patients were informed that the medicine was given to help them eat more. Hypo-

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64. Bruch, H.: Obesity in Childhood: III. Physiologic and Psychologic Aspects of the Food Intake of Obese Children, *Am. J. Dis. Child.* 59:739 (April) 1940.

65. Freyberg, R. H.: *Am. J. M. Sc.* 190:28, 1935.

glycemia is capable of causing great hunger in rats, but the level of blood sugar must be extremely low and continuously so. MacKay and Callaway<sup>66</sup> were unable to make rats fat by injections of regular insulin. It was necessary to maintain continuous and severe hypoglycemia by means of large doses of protamine zinc insulin in order to obtain fat rats. The blood sugar was kept at such a low level that the rats died when deprived of food for four hours. Barnes and Keeton<sup>67</sup> found it necessary to inject huge doses of protamine zinc insulin to obtain obesity. When 32 units per kilogram was injected twice daily, some rats gained 3 to 4 Gm. daily. But food had to be kept before them at all times to prevent death. Even so, the mortality was high.

Such profound degrees of hypoglycemia do not occur spontaneously in human beings, except in the decidedly infrequent cases of hyperinsulinism caused by tumors of the islands of Langerhans. We have recently seen a patient who had had one or more hypoglycemic convulsions every day for ten years. She had learned that eating was the only way to obtain any relief, but it was so short-lived that frequent feedings were essential. She became very obese. Operation disclosed multiple adenomas of the insular tissue.

If the common types of obesity are ever associated with hypoglycemia, the lowering of the blood sugar must be trivial, since it does not cause the classic symptoms of hypoglycemia and there is no evidence that the lesser grades of low blood sugar increase appetite. Furthermore, I am unaware that any one has demonstrated low blood sugar in patients whose main complaint was obesity. The determinations we have made on such patients have failed to reveal a low level of blood sugar in a single instance. On the contrary, hyperglycemia is commonly encountered. In fact, one writer stated that he finds high levels of blood sugar in nearly every patient who has been obese for twenty years.

#### THE FUNDAMENTAL CAUSE OF OBESITY

Many investigators have striven earnestly to discover why human beings become obese. During the era when methods for measuring energy metabolism were being developed, several prominent investigators became convinced, first that the basal metabolism of obese persons was abnormally low, then that their caloric response to food was lessened. However, further study with better methods has demonstrated that the energy performances of the obese person in both these phases are normal. In fact, it is now known that the presence of adiposity increases the total

66. MacKay, E. M., and Callaway, J. W.: *Proc. Soc. Exper. Biol. & Med.* **36**:406, 1937.

67. Barnes, B. O., and Keeton, R. U.: *Am. J. Physiol.* **129**:P305, 1940.



heat production. A fat person requires more food calories than his normal control merely to avoid loss of weight.

As the functions of the endocrine glands came to be understood and their key position was more clearly appreciated, it seemed to many leaders of the medical profession that hypofunction of the pituitary, the thyroid or the gonads offered an adequate explanation of the development of adiposity. But again further study has shown that this is not the cause. *Luxuskonsumption*, lipophilia and hypoglycemia have had the same fate.

These past efforts have not been wasted, however, for they have cleared the field for the acceptance of the doctrine that obesity is invariably caused by an inflow of energy that exceeds the outflow and that this disproportion is brought about by abnormality of the appetite. Excessive eating is an expression of a mood. It is a behavioristic response to a person's environment. This is not the place to attempt an analysis of behavior. For my purpose it will be sufficient to state that conduct is an exceedingly complex blend of hereditary acquisitions modified by earlier environmental experiences. This results in many different types of response by different persons when faced with seemingly identical problems. One person suddenly faced by danger will run from it; the next one will attack it. Physical fatigue causes an insistent desire for food in some persons; other persons suffering from fatigue are repelled by food.

While no attempt is made to discuss the ultimate origins of behavior, the understanding of obesity will be advanced by making a list of proximate causes to which some persons respond (in part) by overeating: (1) overemphasis by a parent of the importance of food in a child's upbringing; (2) gratification obtained from the flavors of foods; (3) the feeling of repose and comfort produced by a full stomach; (4) the temporary respite from anguish caused by intellectual, social or sexual failure; (5) the food habits of youth which are carried over into middle age, even though the need for food is diminished, and (6) disabling disease with its lessened energy requirement which is compensated for by indulgence in food.

#### PREVENTION

Since obesity is an entirely preventable disease, people should be taught how to avoid it. A real effort to acquaint mothers with the dietary needs of their children would be a worth while addition to public health programs. School physicians ought to take the responsibility of teaching children the penalty of overeating. Physicians who are caring for patients suffering from chronic illnesses that limit activity should carefully plan the diet to avoid the insidious acquisition of excessive adipose tissue.

## TREATMENT

Weight can always be reduced by adherence to a restricted diet, but cooperation by the patient is unlikely until the nature of obesity is elucidated and his particular reason for overeating has been discovered and explained to him. The chronicity of his ailment and its lack of immediately disabling features and of severe pain make it so easy to find excuses for delaying treatment or for being lax about it. Most patients are unaware of the threat to life that obesity entails, and they can scarcely be expected to take their condition seriously until they acquire the information.

*Endocrine Medication.*—Thyroid preparations are prescribed by physicians who attribute obesity to hypofunction of the thyroid gland, but it has been pointed out that the metabolic rate with few exceptions is normal and that the twenty-four hour heat production of obese persons is greater than that of persons whose weight is normal. It does not seem wise to burden the patient with the irritability and nervousness of hyperthyroidism and to add to the burden of a circulation already overloaded. Only when the occasional patient is encountered whose basal metabolic rate is pathologically low is thyroid medication justified.

There is serious objection to the administration of any endocrine preparation because the patient, already conditioned by the propaganda of friends and of advertising, is confirmed in his belief that he is the victim of a glandular disease. He is satisfied that the substitution therapy will reduce his weight and that the diet, in spite of the preachments of the physician to the contrary, need not be taken seriously.

*Exercise.*—Exercises of all sorts are widely advocated. These include massage and other passive exercises, but it surely must be realized that the muscular activity indulged in by the attendant is incapable of increasing the heat production of the patient. The latter must do the work if he is to dissipate the energy. But how much can be accomplished by muscular work? The mechanical equivalent of heat is 427 kilogram meters per calory. Since a human being is only about 25 per cent efficient, he will dissipate 3 calories as heat for every calory he converts to work. Accordingly, it will cost him 4 calories to raise 1,000 pounds (454 Kg.) three feet (91 cm.). If he weighs 250 pounds (114 Kg.), he can climb a flight of stairs 10 feet (305 cm.) high at the expense of but 3 calories. But by depriving himself of one third of a gram of butter or one fourth of a teaspoon of sugar, he will reduce his intake 3 calories. He will have to climb twenty flights of stairs to rid himself of the energy contained in one slice of bread! If he is a good walker he may dissipate 100 calories per horizontal mile. Omission of an ounce of cream will reduce the inflow

of calories to the same extent. Since adipose tissue yields 8 calories per gram, the mile's walk will reduce the patient's weight only 12.5 Gm. He must walk 36 miles (58 kilometers) to rid himself of 1 pound (0.5 Kg.) of adipose tissue—how disappointing! Exercise is usually a much harder way of reducing weight than by limitation of food.

Patients who derive pleasure from being muscularly active need not be restricted, provided they are not overtaxing their hearts. Wilder<sup>68</sup> has recently pointed out that some obese patients lose weight more rapidly while they remain in bed than when they are up. He stated the suspicion that they are suffering from lesser grades of passive congestion due to myocardial weakness and that the rapid decline in weight when they are confined to bed is due to loss of edema. Unfortunately, those who enjoy the exercise are also often the ones who acquire a ravenous appetite in the process and find it harder to adhere to a diet when they are active than when they are quiet.

Exercise may be harmful in still another way. When low calory diets are being used, most of the energy expended by the patient will be derived from body fat, and since the organism is restricted in its capacity to oxidize fat completely, this limit may be exceeded. Heat production of about 3,500 calories per twenty-four hours in a person receiving a 450 calory diet may be expected to cause acidosis. The pertinent facts in the most striking example of this condition that my associates and I have witnessed are recorded here:

Miss B., 24 years old and 5 feet 6½ inches (168 cm.) tall, weighed 289 pounds (131 Kg.) when she was admitted to the hospital for the treatment of obesity. During the next four weeks she was studied intensively on several reduction diets and was then placed on a diet that yielded 450 calories and consisted of protein 60 Gm., fat 10 Gm. and carbohydrate 30 Gm. Twenty days later, when her weight had fallen to 269 pounds (122 Kg.), she secured a room near the hospital but continued to come to the hospital for her diet. Since she enjoyed walking and knew that exercise would hasten the loss of weight, she strolled about considerably and gradually increased the length of the walks. One day she was on her feet, walking and shopping for eight hours. Late that afternoon, for the first time, she felt fatigued and had no desire for food. Nevertheless, she continued her activities that evening. Next morning she had no complaints but refused most of the noon meal and all of the evening one. By 10:30 p. m. she was definitely nauseated. She drank some orange juice but vomited it. She slept well that night. The third day she had no desire for food and ate little. That evening she felt ill generally. The fourth and the fifth day she stayed in bed and ate nothing. By the sixth morning she was so nauseated that she vomited every time she ate. Her vision was blurred; she had a pain in the pit of the stomach, and she was short of breath. These symptoms increased during the day, especially the nausea. And then for the first time, she reported her difficulties to her physician, who moved

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68. Wilder, R. M.; Smith, F. H., and Sandiford, I.: *Ann. Int. Med.* 6:724, 1932.

her into the hospital and gave her an intravenous injection of 3,000 cc. of a 5 per cent solution of dextrose in water. By the next morning she was still nauseated and fatigued, but the other symptoms were gone. Twenty-four hours later she felt quite well again.

*Diet.*—There is a considerable difference of opinion about how many calories the reduction diet should contain. Some authors have expressed the opinion that patients are less liable to cheat when only moderate restriction is prescribed. Our own experience has led my associates and me to the opposite conclusion. The slow loss of weight that accompanies the more liberal plans is so discouraging that the patients often give up the diet after a few months. We, like Evans,<sup>69</sup> have had most success when we have limited the calories sharply. The fear that the small diet will not maintain nitrogen balance has been set aside by Strang and McClugage.<sup>16</sup> They have shown that obese patients who subsisted on 450 calories daily were always in nitrogen balance when the diet contained 60 Gm. of protein. By choice, we prescribe a similar diet.

*Selection of Food*<sup>70</sup>.—The reduction diet requires the use of milk, eggs, meat and meat substitutes, fruits and vegetables and whole wheat bread or whole grain cereal. Simple cookery is desirable, and the food should be prepared without the addition of fat. It is our experience that the dietary habits of obese people may be characterized not by an intake of a large quantity of food but rather by the use of moderate quantities of foods with a high caloric value. In the instruction of an obese patient, it is a simple matter to teach him to omit sugar because sweet flavors are not easily disguised. It is also relatively simple to teach him to limit the use of foods high in starch. Restricting of the intake of fat is a more difficult matter which requires special precautions in preparation and in cookery. The use of so-called "dietetic food" is usually not necessary.

The foods commonly used in low calory diets will be discussed here.

*Milk:* It is a good practice to use a pint of whole milk for each diet of 1,000 calories or over. Half of a large can of evaporated milk has the same food value as a pint of fresh milk. A pint of skimmed milk or of buttermilk has half the caloric value of a pint of whole milk and is used for diets containing less than 1,000 calories. Skimmed or separated milk obtained from the dairy contains only about 0.1 per cent fat. Pouring the cream layer from a bottle of milk will not give a product as low in fat as the dairy skimmed milk.

*Meat and Meat Substitutes:* Two servings each day should be used. Beef, veal, lamb and fowl are prepared by broiling, roasting and boiling.

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69. Evans, F. A.: Tr. A. Am. Physicians 53:352, 1938.

70. Frances MacKinnon, dietitian, University Hospital, guided me in the preparation of this section.

Lean cuts should be selected. The fat content is determined both by the type of animal and by the region of the body, as will be seen in table 19. The methods used for preparing meat are suitable also for fish. Fat is removed from canned salmon or tuna by scalding it with boiling water. Since shell fish are lower in calories than meats, their use should be

TABLE 19.—*Fat Content per Hundred Grams of Various Foods\**

0.1 to 2 %	2 to 5 %	5 to 10 %	10 to 15%
<b>Fish</b>	<b>Fish</b>	<b>Fish</b>	<b>Fish</b>
Bass	Bluefish	Butterfish	Halibut, smoked
Carp	Halibut steak	Eel	Herring, canned
Cod	Mackerel, horse	Herring, Atlantic	Mackerel, Atlantic
Croaker		Lake trout	Mackerel, Spanish
Finnan haddie, smoked	Chicken	Salmon, canned	Salmon, Atlantic
Flounder, southern	Light meat	Shad	
Haddock	Dark meat		Lamb
Whiting	Gizzard	Duck, domestic	Ohops
Perch	Liver	Muscle	Shoulder, lean
Pickrel			
Pike	Duck, wild	Turkey	Beef
Porgy	Muscle	Dark meat	Neck, very lean
Red snapper	Gizzard		Rib, very lean
Smelt		Rabbit, domestic	Roast, lean
Sole	Turkey	Muscle	Sirloin
Sturgeon	Light meat		Tenderloin
	Liver	Veal	Tongue, lean
<b>Shellfish</b>		Loin	
Clam	Rabbit, wild	Rib, lean	Venison
Crab	Muscle	Round, lean	Side and hind
Crayfish		Rump, lean	quarter
Frog legs	Veal		
Lobster	Kidney	Lamb	
Mussels	Liver	Leg, lean	
Oysters	Sweetbread		
Scallops	Tongue	Beef	
Shrimp		Brains	
	Lamb	Chuck, lean	
<b>Miscellaneous</b>	Liver	Corned beef, very lean	
Cottage cheese	Kidney	Dried beef	
Tripe		Foreshank	
	Beef	Hindshank	
	Liver	Kidney	
		Round, lean	
	Pork		
	Kidney	Venison, lean	
	Liver	Goose, muscle	
		Guinea hen	
		Quail	

\* Adapted from Chatfield, O., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, U. S. Dept. of Agriculture, June, 1940. Articles high in fat have been omitted.

emphasized. Cottage cheese is the only cheese suitable for use in a diet with restricted calories; other varieties contain as high a percentage of fat as medium fat meat. Eggs should be boiled or poached to avoid the fat which is ordinarily used when they are fried or scrambled.

Vegetables (table 20): For diets of 800 calories or over it is well to prescribe at least three servings per day, one serving to be eaten raw. For diets of 800 calories or less, the vegetables can be chosen only from the 3 per cent and the 6 per cent list. Because of their vitamin and mineral values the daily use of leaves, stems or pods with a green color should be

stressed. In the cooking or serving of vegetables it is usual to add some form of fat. In the southern states salt pork is used in the cooking of greens and green beans. In the North butter is added to vegetables

TABLE 20.—*Fruits and Vegetables Classified According to Their Average Calorific Values per Hundred Grams\**

16 Calories "3 per cents" Carbohydrate, 3 Gm. Protein, 1 Gm.  Vegetables Asparagus Bamboo shoots Beans, green † Beans, wax † Bean sprouts Beet greens Broccoli Cabbage Cabbage, Chinese Cauliflower Celery Chard Chicory Cress, water Cucumbers Endive Escarole French endive Lettuce Mustard greens Radishes Sauerkraut Sorrel Spinach Squash, summer Tomatoes Tomato juice Turnip tops  Fruit Rhubarb	28 Calories "6 per cents" Carbohydrate, 6 Gm. Protein, 1 Gm.  Vegetables Carrots, canned Collards Dandelion greens Eggplant Kale Kohlrabi Leeks Lamb's quarters Okra Parsely Peppers Pumpkin Squash, winter Turnips  Fruits Blackberries Melons Strawberries	40 Calories "9 per cents" Carbohydrate, 9 Gm. Protein, 1 Gm.  Vegetables Brussel sprouts Beets Carrots, fresh Onions, fresh Peas, canned † Rutabagas  Fruits Applesauce, canned, unsweetened Apricots, water-packed Blueberries Cranberries Gooseberries Grapefruit Grapefruit juice Peaches Pears Loganberries Limes Lemons Raspberries Tangerines
52 Calories "12 per cents" Carbohydrate, 12 Gm. Protein, 1 Gm.  Vegetables Lima beans, green, canned †	64 Calories "15 per cents" Carbohydrate, 15 Gm. Protein, 1 Gm.  Vegetables Parsnips Kidney beans, red, canned † Peas, fresh †	96 Calories "18 per cents" Carbohydrate, 18 Gm. Protein, 4 Gm.  Vegetables Corn, canned, sweet Potatoes  Fruits Prune juice Figs, fresh Grape juice Pomegranates
Fruits Apricots, fresh Cherries, sour, fresh Oranges Orange juice Pineapple Plums Kumquats	Fruits Huckleberries Grapes Mangos Nectarines	

\* Adapted from Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, U. S. Dept. of Agriculture, June, 1940.

Since tables like this were devised originally for use in prescribing diabetic diets, the foods are usually referred to in terms of the carbohydrate content. Thus any item in the first column is spoken of as a "3 per cent," not as a "16 calory" food.

† The protein content of these foods is distinctly higher than 1 Gm. per cent. Accordingly, they should either be omitted when weighed diets are prescribed or the additional calories should be taken into account. Green beans and wax beans contain 2.5 per cent protein, canned peas 4 per cent protein, canned green lima beans 5 per cent protein, canned red kidney beans 6 per cent protein and fresh peas 7 per cent protein.

before they are sent to the table. The people of southern Europe and Asia Minor cook vegetables in olive oil. Hence, obese patients should

be instructed that steaming, baking or boiling vegetables in salted water are the only methods of preparation to be used and that the vegetables should be served without the addition of fat.

Fruits (table 20): It is desirable to include two servings of low calory fruits each day, and preferably both should be eaten raw. Of the canned fruits, only those which are juice packed or water packed are suitable for use. In areas where housewives can their own fruit, it is a simple matter to add only water to the fresh fruits before the jars are processed. Contrary to popular opinion, a sugar syrup does not prevent spoilage of the fruit.

Bread: Since the refined bread flours have been deprived of the vitamins and minerals present in the whole seeds, it is desirable to urge the use of whole grain breads. However, since bread is a concentrated food, none of it is included in the 450 calory diet (table 21) and only one slice is prescribed in the 600 and the 800 calory diet (tables 22 and 23). Under such circumstances, even whole grain bread would be an unimportant source of vitamins. Furthermore, many patients dislike to eat whole grain bread. Fortunately, they can now obtain a product of nearly equal value in the form of "enriched" bread.

Fats: It is important to instruct the patient carefully with regard to the amount of fat which is to be added to his food. Butter or fortified margarines are the preferable forms to use, because even a small amount will add some vitamin A, while the meat fats and vegetable oils are devoid of this vitamin. For use in low calory diets, there are some palatable butter substitutes which are calory free.

Other Foods: Since clear tea and coffee, mushrooms and the soup made from bouillon cubes contain no calories, they can be used in any quantity desired. Saccharin is satisfactory as a sugar substitute. Salt, condiments and vinegar may be used as seasoning.

Since it is believed that the epigastric distress of which many patients complain is due to emptiness of the stomach, it is important to consider the distribution of the food. Even though three meals a day may not always conform to the patient's previous food habits, he will find that he gets hungry less frequently if he eats at least three times a day. Protein requires several hours of gastric digestion and therefore slows the emptying time of the stomach. The use of a food high in protein at each meal, such as an egg for breakfast and meat, fish or cottage cheese at luncheon and dinner, will keep the patient from having sharp hunger pains an hour or two after meals. If the meals are more than four hours apart, a quart of skimmed milk or buttermilk may be substituted for a pint of whole milk in the day's allowance and a glass of milk used at an interval half way between each two meals and at bedtime.

The matter of the measurement of portions calls for some comment. It is our experience that the use of dietetic scales, which weigh the food

in grams or ounces, is the best solution for a trying problem. These scales are simple to use, and food may be weighed directly in serving dishes without the extra handling necessitated by the use of cups. There are several inexpensive dietetic scales on the market, and usually they can be resold when the patient has completed his reduction of weight. The other and more commonly used method is prescribing foods in the ordinary household measure: cups, tablespoons and teaspoons. For many cooked vegetables, such as greens, tomatoes and diced root vegetables, measuring with a cup is satisfactory. For asparagus, broccoli, whole

TABLE 21.—*Reduction Diet, Four Hundred and Fifty Calories*  
Protein 60 Gm., Fat 9 Gm. and Carbohydrate 32 Gm.

Menu Plan	
Breakfast:	
6 per cent fruit.....	100 Gm.
Skimmed milk.....	200 Gm.
Coffee.....	Ad libitum
Luncheon:	
Meat or fish.....	60 Gm. cooked
3 per cent vegetable.....	100 Gm.
Skimmed milk.....	100 Gm.
Dinner:	
Meat or fish.....	90 Gm. cooked
3 per cent vegetable.....	100 Gm.
Skimmed milk.....	100 Gm.
Sample Menu	
Breakfast:	
Melon.....	100 Gm.
Skimmed milk.....	200 Gm.
Coffee.....	Ad libitum
Luncheon:	
Boiled shrimp *.....	100 Gm.
Lettuce and tomato salad.....	100 Gm.
Skimmed milk.....	100 Gm.
Coffee.....	Ad libitum
Dinner:	
Lean corned beef.....	90 Gm. cooked
String beans.....	60 Gm. cooked
Cole slaw (raw cabbage with vinegar and seasonings).....	40 Gm.
Skimmed milk.....	100 Gm.
Coffee.....	Ad libitum

\* Note that 100 Gm. of shellfish has the caloric value of 60 Gm. of lean meat or fish.

beets or baked squash, attempting to measure with a cup spoils the appearance of the vegetable. It is almost impossible to measure raw vegetables satisfactorily, and the use of terms such as "medium" or "small" is leaving the size of the portion to the patient's judgment. It is also difficult to describe the sizes of servings of raw fruits, although one may use the diameters of round fruits or number of berries or grapes. The greatest difficulty arises in teaching the patient the sizes or portions of meat. Wax food models are helpful, but they are expensive and difficult to secure. However, for diets of 800 calories or more, the use of household measures and descriptive terms may suffice. When diets with fewer calories are prescribed, the patient needs a dietetic scale to insure precision in measuring portions.



*Diet Prescriptions.*—The plan for a diet restricted to 450 calories will be found in table 21. It also shows the selection and distribution of the actual food for one day. It will be noted that green leaves and fruits are emphasized. The bulk thus afforded compensates partly for the meagerness of the diet, and, of equal importance, these foods are excellent sources of the vitamins. However, any possible insufficiency of vitamins should be guarded against by prescribing additional amounts of the vitamin B complex. The 400 Gm. of skimmed milk supplies nearly

TABLE 22.—*Reduction Diet, Six Hundred Calories*  
Protein 65 Gm., Fat 9 Gm. and Carbohydrate 65 Gm.

Menu Plan	
<b>Breakfast:</b>	
6 per cent fruit.....	100 Gm.
Bread.....	30 Gm.
Skimmed milk.....	100 Gm.
Coffee.....	Ad libitum
<b>Luncheon:</b>	
Meat or fish.....	60 Gm. cooked
3 per cent vegetable.....	100 Gm.
6 per cent fruit or vegetable.....	100 Gm.
Skimmed milk.....	200 Gm.
<b>Dinner:</b>	
Meat or fish.....	90 Gm. cooked
3 per cent vegetables	
1 raw.....	100 Gm.
1 cooked.....	100 Gm.
9 per cent fruit or vegetable.....	100 Gm.
Milk.....	100 Gm.
Tea or coffee.....	Ad libitum
Sample Menu	
<b>Breakfast:</b>	
Melon slices.....	100 Gm.
Bread, toasted, dry.....	30 Gm.
Skimmed milk.....	100 Gm.
Coffee.....	Ad libitum
<b>Luncheon:</b>	
Cottage cheese with olives.....	90 Gm.
Head lettuce (dressed with tarragon vinegar and condiments).....	100 Gm.
Raspberries.....	70 Gm.
Skimmed milk.....	200 Gm.
<b>Dinner:</b>	
Ground beef patty, broiled.....	100 Gm.
Beet greens with lemon.....	100 Gm. cooked
Sliced tomato.....	100 Gm.
Peaches, water-packed.....	100 Gm.
Skimmed milk.....	100 Gm.
Coffee.....	Ad libitum

0.5 Gm. of calcium, which is sufficient for an adult, and at the same time serves as a source of excellent protein. Practically all of the 60 Gm. of the protein prescribed are of animal origin. The fluid intake is not limited, since large amounts of liquid do not cause retention of water and restriction of fluids does not prevent it.

A diet of this type causes a loss of 3 to 5 pounds (1.3 to 2.3 Kg.) a week, on the average. The patient may be assured that he will lose 50 pounds (23 Kg.) in three or four months. After a few weeks when he is convinced that he is really losing at the promised rate, he finds it less trying to continue the plan. It is harder to follow a diet at home

than in the hospital where the food is put before the patient as a matter of course and without any expression of sympathy. This is especially true for the housewife who is responsible for feeding the family. The preparation of meals whets her appetite, and she must display great

TABLE 23.—*Reduction Diet, Eight Hundred Calories*  
Protein 73 Gm., Fat 28 Gm. and Carbohydrate 65 Gm.

Menu Plan		
	Household Measure	Weight, Gm.
Breakfast		
6 per cent fruit.....	1 serving	100
Egg.....	1	50
Bread.....	1 slice	30
Butter.....	1 teaspoon	5
Luncheon:		
Meat or fish.....	2 oz.	60
3 per cent vegetable.....	1 serving	100
6 per cent fruit or vegetable.....	1 serving	100
Skimmed milk.....	1 glass	200
Butter.....	1 teaspoon	5
Dinner:		
Meat or fish.....	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked).....	2 servings	200
9 per cent fruit or vegetable.....	1 serving	100
Skimmed milk.....	1 glass	200
Butter.....	1 teaspoon	5
Sample Menu		
Breakfast:		
Strawberries.....	½ cup	90
Poached egg.....	1	50
Whole wheat toast.....	1 slice	30
Butter.....	1 teaspoon	5
Black coffee.....	Ad libitum	Ad libitum
Luncheon:		
Crab meat salad:		
Diced celery.....	¼ cup	60
Crab meat.....	½ cup	120
Minced onion and lemon		
Lettuce leaves		
Mayonnaise *.....	1 tablespoon	15
Melon.....	1	60
Skimmed milk.....	1 glass	200
Dinner:		
Beef steak, broiled.....	3 oz.	90
Asparagus.....	6 stalks	100
with butter.....	2 teaspoons	10
Lettuce salad:		
Lettuce.....	⅓ head	50
Tomato.....	1 small	100
Dressing *.....	Ad libitum	Ad libitum
Pear.....	½ cup	120
Skimmed milk.....	1 glass	200

\* Ingredients: 1 egg, 1 teaspoon salt, 1 teaspoon mustard, 2 cups liquid petrolatum, 2 table-spoons vinegar and ⅓ teaspoon paprika.

fortitude not to overstep her own meager allowance. For these reasons we urge the patients to experience the first two or three weeks of food restriction in the hospital. This also gives them the opportunity to acquire some information about the selection of food from the instruction provided for them.

When the need to lose weight is urgent, as, for example, in heart disease, we have not hesitated to restrict the diet to 300 calories. The patient in figure 10 was intensely dyspneic and deeply cyanotic when he

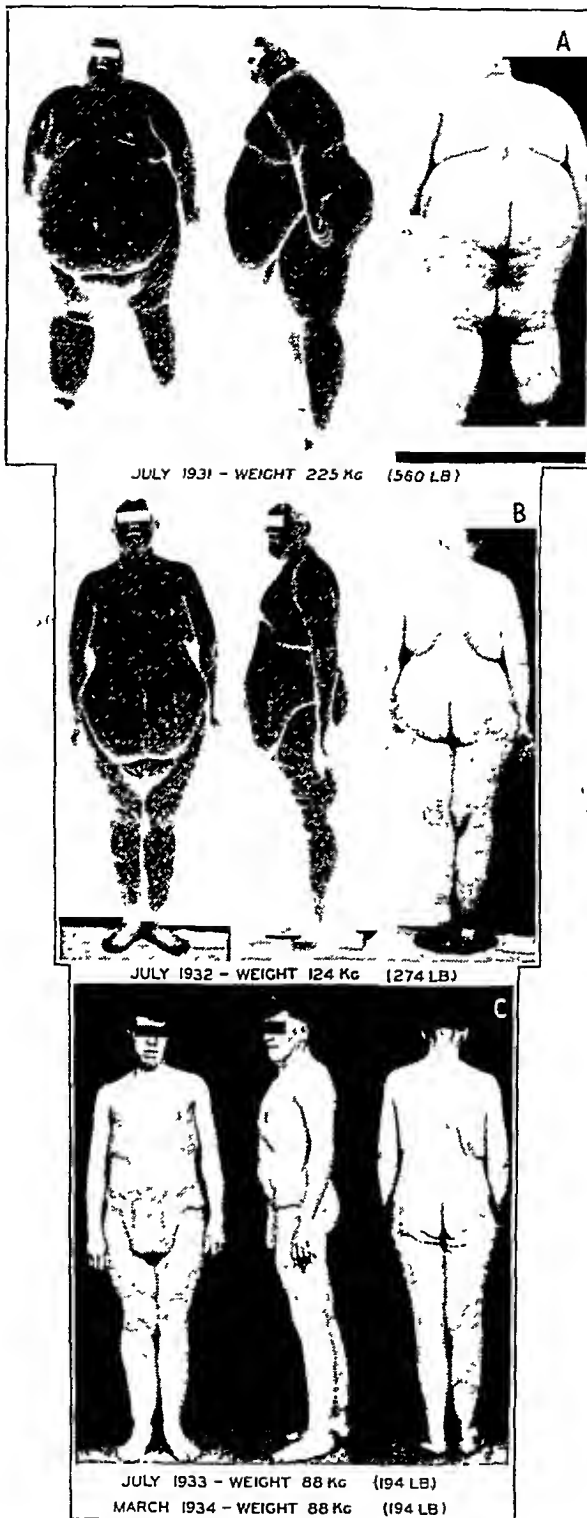


Fig. 10.—*A*, extreme obesity characterized by firm masses of adipose tissue. *B*, the same patient one year later. Dietary restriction has caused a loss of 286 pounds. The masses of adipose tissue are much smaller. *C*, the same patient after two years of dietary restriction. The total loss of weight was 366 pounds. The masses of adipose tissue are gone.

appeared for treatment. The circumscribed masses of adipose tissue in the pubic region and above the knees should be noted for they, together with the pain expressed in his face, would lead some clinicians to make a diagnosis of adiposis dolorosa (Dercum's disease). He was placed on a diet that contained 25 Gm. of protein and 300 calories. There was no

TABLE 24.—*Reduction Diet, One Thousand Calories*  
Protein 75 Gm., Fat 42 Gm. and Carbohydrate 85 Gm.

Menu Plan		
	Household Measure	Weight, Gm.
<b>Breakfast</b>		
6 per cent fruit.....	1 serving	100
Egg.....	1	50
Bread.....	1 slice	30
Butter.....	1 teaspoon	5
Coffee ad libitum, with milk.....	1 oz.	30
<b>Luncheon:</b>		
Lean meat, fish.....	2 oz.	60
or		
Cottage cheese.....	3 oz.	90
3 per cent vegetable.....	1 serving	100
6 per cent fruit or vegetable.....	1 serving	100
Bread.....	1 slice	30
Butter.....	1 teaspoon	5
Whole milk.....	1 glass	200
<b>Dinner:</b>		
Lean meat or fish.....	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked).....	2 servings	200
9 per cent fruit.....	1 serving	100
Whole milk.....	1 glass	200
Tea or coffee.....	Ad libitum	Ad libitum
<b>Sample Menu</b>		
<b>Breakfast:</b>		
Strawberries.....	½ cup	100
Bolled egg.....	1	50
Whole wheat toast.....	1 slice	30
Butter.....	1 teaspoon	5
Coffee with milk.....	1 oz.	30
<b>Luncheon:</b>		
Cottage cheese.....	3 tablespoons	65
Kale.....	½ cup	100
Cabbage and celery salad.....	½ cup	100
Mineral oil dressing.....	1 tablespoon	15
Whole wheat bread.....	1 slice	30
Butter.....	1 teaspoon	5
Whole milk.....	1 glass	200
<b>Dinner:</b>		
Roast beef, fat trimmed.....	3 oz.	90
Broccoli.....	½ cup	100
Cucumber and radishes.....	¼ cup	50
Pear.....	1	125
Whole milk.....	1 glass	200
Black coffee.....	Ad libitum	Ad libitum

other treatment except rest. The excretion of nitrogen was about twice the intake of it. He adhered faithfully to this diet for one year, during which time he lost 286 pounds (130 Kg.). During the second year, he received 600 calories and lost another 80 pounds (36 Kg.). He had now returned to approximately normal weight. In the interval his gluttonous habits had been abolished, so that he continued to weigh 194 pounds (88 Kg.) without any effort to restrict his intake of food.

A few patients whose circumstances require them to work hard physically claim that the 450 calory diet reduces their strength so much

that they cannot continue their occupations unless they get more to eat. When we are convinced that they have given the diet an honest trial and that they cannot be persuaded to continue it some additional food is allowed. Often such patients can be satisfied with 600 calories arranged according to the plan in table 22. Still other patients cannot be persuaded to adhere to a diet unless they are allowed 800 or even 1,000 calories (tables 23 and 24).

The treatment of obesity in children must emphasize behavior rather than diet. It has been pointed out that these children have not learned to obey and that often they are pampered and uncooperative. It is an integral part of the treatment to teach them to control their whims and desires and to help them develop a sense of proportion. The younger children need to be trained to eat food that is wholly adequate for them without reduction of the energy content much below the requirement of normal children of the same height and age. Sharp underfeeding may be too great a load when coupled with the correction of behavior. If the calories of the diet are adjusted to stop further gain in weight, the obesity will gradually disappear as height increases. Later on, when the child has become adjusted to the discipline, a further reduction in calories may be arranged if there is still much extra fat to be removed.

## News and Comment

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1943 Annual Session of American College of Physicians Canceled.—The Board of Regents of the American College of Physicians has announced the cancellation of the 1943 annual session, which was scheduled to be held in Philadelphia April 13 to 16. This action was taken after thoughtful consideration of all factors involved, including an intimation from the Secretary of War and the Office of Transportation that large national medical groups should not plan meetings at the time set. The president has announced that all other activities of the College will be pursued with even greater zeal. The College will especially promote regional meetings over the country and will organize postgraduate seminars in the various military hospitals for physicians in the armed forces.

## Book Reviews

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**Blood Grouping Technic.** By Fritz Schiff, M.D., and William C. Boyd, Ph.D., with a foreword by Karl Landsteiner. Price, \$5. Pp. 248. New York: Interscience Publishers, Inc., 1942.

The authors of this monograph are well qualified, as indicated by Landsteiner in the foreword. The book is divided into three parts: "Theoretic Foundation of Blood Grouping," "General Technic of Blood Group Investigation" and "Special Application of Blood Grouping Technics." The subjects are clearly and briefly discussed with the idea of aiding clinicians, serologists, anthropologists and workers in legal and in military medicine. Not only is the material presented clearly from a theoretic point of view, but it is presented practically, including the technics for typing blood for transfusions and for establishing paternity. The chapters, subchapters and paragraphs are numbered, so that by merely referring to the table of contents one can easily find any aspect of a subject. A fairly complete bibliography follows each subchapter for those who might be interested in further details of the original observations. There is a good index in addition to the rather complete table of contents.

This monograph will be appreciated by every one and is to be recommended not only as a reference book but as a book worth reading to learn much about blood types and typing technics and their practical applications.

**The Ophthalmic Formulary.** By G. Griffin Lewis, M.D., F.A.C.S. Price, \$3.50. Pp. 167. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

The compilation of "favorite prescriptions of prominent oculists from all parts of the world" is a handy gadget to have on the desk for an oculist who wonders what a distinguished colleague might prescribe for a given disease of the eye. Most of the formulas contained in this volume have the venerability of age and long usage and will stand the test of pharmacologic compatibility. A few will stand the test of therapeutic experience.

The name of a sponsor appears with every prescription. It is not claimed that the sponsor originated the formula or is responsible for the spelling or the accuracy of the dose. The purpose of the name is not clear, but one may assume that it implies that the formula was one of his favorite prescriptions.

Indications for use of the various prescriptions are given in a general way. Contraindications are not mentioned. The manual is useful as a crib from which a lazy physician may select and prescribe a remedy for a condition which he hopes he has diagnosed correctly (for otherwise the book fails to rescue him from his dilemma). It may also lend moral support to his efforts in treatment of diseases of the eye. In most instances he will find that the sponsor's name is as useful as the formula.

**The Pathology of Trauma.** By Alan Richards Moritz. Price, \$6. Pp. 386, with 117 engravings. Philadelphia: Lea & Febiger, 1942.

As the publisher states, this book is designed to bridge the gap between the various pathologic and clinical disciplines dealing with trauma. The subject is thoroughly covered; after general chapters traumatic lesions of every system of the body are dealt with. As a matter of fact, the subject is treated so extensively that little space is available for individual subjects. No less important a matter than penetrating wounds of the thorax is, for example, discussed in one page. The illustrations are excellent and the bibliography representative.

# INDEX TO VOLUME 70

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.

**Abdomen:** See Gastrointestinal Tract  
**Abnormalities and Deformities:** See under names of organs and regions  
**Abscess:** See under names of organs and regions  
**Acid, Ascorbic:** See Ascorbic Acid  
**Adams, W. E.:** Experimental production of emphysema, 379  
**Adipose Tissue:** See Obesity  
**Adlersberg, D.:** Uric acid partition in gout and in hepatic disease, 101  
**Age, Interrelation of factors influencing mortality in diabetic coma; statistical study,** 369  
**Ainhum,** 471  
**Air, disinfection of,** 174  
**Air Passages:** See Respiratory Tract  
**Altshuler, S. S.:** Maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
**Amino Acids, maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies,** 749  
**Amputations,** 508  
**Amyloidosis, congo red test for amyloid disease; quantitative technic,** 416  
 utility of congo red test in diagnosis and in differential diagnosis, 421  
**Anemia, refractory hemolytic anemia; report of 5 cases in which treatment was with splenectomy,** 11  
 use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722  
**Anesthesia, mechanism of pentothal sodium antidiuresis,** 567  
**Aneurysm, 499**  
 aortic, as cause of obstruction of venous circulation of mediastinum, 893  
 aortic; rupture into pulmonary artery, 893  
 incomplete rupture of aorta; heretofore unrecognized stage of dissecting aneurysm and cause of cardiac pain and cardiac murmurs, 689  
 of pulmonary artery, 339  
**Anoxemia:** See Oxygen, deficiency  
**Anthrax; review of 60 cases, with report on therapeutic use of sulfonamide compounds,** 785  
**Aorta, Aneurysm:** See under Aneurysm  
 incomplete rupture; heretofore unrecognized stage of dissecting aneurysm and cause of cardiac pain and cardiac murmurs, 689  
 syphilis; diagnosis of uncomplicated syphilitic aortitis, 888  
 syphilis; gummatous aortitis, 396  
 syphilis; syphilitic aortic regurgitation, 891  
 syphilis; syphilitic aortitis in congenital syphilis, 911  
**Aortitis, Syphilitic:** See Aorta, syphilis  
**Apparatus, experimental production of emphysema,** 379  
**Appendicitis,** 672  
**Appetite and hunger,** 1076  
 inaccuracy of, 1079  
**Arachnoid, surgical treatment of optic chiasm arachnoiditis,** 905  
**Armies:** See Medicine, military  
**Arrhythmia:** See also Heart, block; Heart, rate  
 auricular fibrillation, 324  
 cardiac arrhythmias, 323  
 Hubbard's syndrome, 324

**Arrhythmia—Continued**  
 use of potassium salts in cardiac arrhythmias, 325  
 ventricular fibrillation, 323  
**Arsenic and Arsenic Compounds, hypersensitivity to arsenicals,** 872  
 Therapy: See Syphilis  
**Arsphenamines:** See under Syphilis  
**Arteries:** See also Aneurysm; Aorta; Arteriosclerosis; Blood pressure; Blood vessels; Embolism; Periarteritis; Pulse; Thrombosis; Vasomotor System; etc.  
 Inflammation: See also Periarteritis  
 inflammation; temporal arteritis, 474  
 rupture of aortic aneurysm into pulmonary artery, 893  
**Arteriosclerosis, 464**  
 coronary arteriosclerotic heart disease, 335  
 induced anoxemia in patient with coronary arteriosclerotic heart disease, 337  
**Arteritis:** See Arteries, inflammation  
**Ascorbic Acid and arsenical sensitivity,** 872  
**Asthma, neurocirculatory, heart in wartime with reference to,** 303  
**Auricular Fibrillation:** See Arrhythmia  
**Auscultation,** 317  
**Bacilli:** See Bacteria  
**Bacteria:** See also Meningococci; Staphylococci; Streptococci; Viruses; etc.  
 antibiotic agents, 175  
**Diphtheria:** See Diphtheria  
**Dysentery:** See Dysentery  
 gas bacillus infection, 148  
**Shigella:** See Dysentery  
**Tularensis:** See Tularemia  
**Bejel:** See Syphilis  
**Berk, J. E.:** Effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959  
**Bessey, O. A.:** Production and study of cardiac failure in thiamine-deficient pigeons, 763  
**Bismuth and Bismuth Compounds:** See also Syphilis  
 untoward effects of bismuth therapy, 868, 874  
**Bladder, neurogenic,** 903  
**Blood:** See also Hemoglobin and Hemoglobin Compounds  
 Circulation: See Arteries; Cardiovascular System; Heart; Vasomotor System; etc.  
 Diseases: See Anemia; etc.  
 flow, measurement of, 448  
 nitrogen; interrelation of factors influencing mortality in diabetic coma; statistical study, 369  
 pressure, abnormalities of, 481  
 pressure, high; arterial hypertension, 332  
 pressure, high; clearance of diodrast, phenol-sulfonphthalein and inulin in hypertension and in nephritis, 935  
 pressure, high; cold pressor phenomena, 482  
 pressure, high; counterpressor mechanism, 492  
 pressure, high; critical statistical analysis of data on renal function in grouped subjects with essential hypertension, 948  
 pressure, high; endocrine hypertension, 487  
 pressure, high; experimental hypertension, 487  
 pressure, high; function of separate kidneys in hypertensive subjects, 738  
 pressure, high; hyperactive vasodepressor carotid sinus reflex, 983  
 pressure, high; medical therapy of hypertension, 493



## Blood—Continued

- pressure, high; pyclo nephritis and hypertension; study of their relation in 11,898 necropsies, 284
- pressure, high; surgical treatment of hypertension, 505
- pressure, high; syphilis and hypertension, 913
- pressure, high; vascular phase of chronic diffuse glomerulonephritis; clinicopathologic study, 260
- pressure; interrelation of factors influencing mortality in diabetic coma; statistical study, 369
- pressure, low; orthostatic circulatory insufficiency in tabes dorsalis, 905
- pressure, measurement of, 315
- sodium *d*-lactate tolerance as test of hepatic function, 829
- sugar; hypoglycemia and obesity, 1083
- sugar; interrelation of factors influencing mortality in diabetic coma; statistical study, 369
- transfusion of conditioned universal blood; clinical observations, 1
- Vessels: See also Arteries; Cardiovascular System; Periarthritis; Vasomotor System; etc.
- vessels, vascular diseases; eighth annual review, 444
- vessels; vascular injuries, 498
- Body, psychosomatics, 1019
- Bones, syphilis, 875

## BOOK REVIEWS:

- Acute Alcoholic Intoxication: Critical Review; H. W. Newman, 346
- Annual Review of Physiology; J. M. Luck and V. E. Hall, 181
- Arthritis and Allied Conditions; B. I. Comroe, 345
- Arthritis in Modern Practice: Diagnosis and Management of Rheumatic and Allied Conditions; O. Steinbrocker, 687
- Biology of Negro; J. H. Lewis, 512
- Blood Grouping Technique; F. Schiff and W. C. Boyd with foreword by K. Landsteiner, 1098
- Breathing Capacity and Grip Strength of Preschool Children; E. Metheny, 180
- Clinical and Experimental Investigations on Genital Functions and Their Hormonal Regulation; B. Zondek, 182
- Complete Weight Reducer; C. J. Gerling, 918
- Dermatologic Therapy in General Practice; M. Sulzberger and J. Wolf, 512
- Diseases of Metabolism; edited by G. G. Duncan, 687
- Enfermedad reumatica; D. Urrutia M. and S. Vaisman B., 345
- Epilepsy and Cerebral Localization: Study of Mechanism, Treatment and Prevention of Epileptic Seizures; W. Penfield and T. C. Erickson, with special chapters by H. W. Jasper and M. R. Harrower-Erickson, 916
- Eye Manifestations of Internal Diseases; I. S. Tassman, 512
- From Witchcraft to Chemotherapy: Linacre Lecture 1941; W. Langdon-Brown, 688
- Lymphatic System, Its Part in Regulating Composition and Volume of Tissue Fluid: Lane Medical Lectures; C. K. Drinker, 181
- Manual of Pharmacology and Its Applications to Therapeutics and Toxicity; T. Sollmann, 512
- Occupational Diseases: Diagnosis, Medical Legal Aspects, and Treatment; R. T. Johnstone, 918
- Occupational Tumors and Allied Diseases; W. C. Hueper, 918
- Ophthalmic Formulary; G. G. Lewis, 1098
- Paroxysmalnaya Tachycardia; M. E. Mandelstam, 917
- Pathology of Trauma; A. R. Moritz, 1098
- Personality and Mental Illness; J. Bowlby, 346

## BOOK REVIEWS—Continued

- Pharmacology of Anesthetic Drugs; J. Adriani, 180
- Prothrombin: su valor clinico; A. Gorodner, 182
- Psychosurgery: Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders; W. Freeman and J. W. Watts, 179
- Religion in Illness and Health; C. A. Wise, 688
- Synopsis of Ano-Rectal Disease; L. J. Hirschman, 917
- Synopsis of Materia Medica, Toxicology and Pharmacology; F. R. Davison, 688
- Trastornos cardiacos en los estados anemicos; E. R. Picrafesa, 182
- Tumores primitivos malignos bronco-pulmonares; J. Palacio and E. S. Mazzei, 181
- Wounds and Fractures; H. W. Orr, 182
- Brain: See also Hypothalamus; Meninges; Nervous System; etc.
- Diseases: See Encephalitis
- electroencephalography, 1030
- encephalographic studies in neurosyphilis, 896
- neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236
- Branch, C. F.: Polycythemia vera; report of case, 919
- Bright's Disease: See Nephritis
- Cancer: See under names of organs and regions, as Colon; Stomach; etc.
- Carbon Dioxide transportation, 315
- Carbon Monoxide poisoning, 314
- Cardiovascular System: See also Arteries; Blood vessels; Heart; Vasomotor System; etc.
- syphilis, 888
- Carotid Sinus, hyperactive vasodepressor carotid sinus reflex, 983
- syndrome, 500
- Cerebrospinal Fluid, protein, composition of, 906
- Charcot Joint: See Tabes Dorsalis
- Chasis, H.: Function of separate kidneys in hypertensive subjects, 738
- Chemotherapy, 133. See also under names of diseases, as Cholera; Dysentery; Empyema; Endocarditis; Malaria; Meningitis; Pneumonia; Rheumatic Fever; Scarlet Fever; etc.
- Cheney, G.: Cinchophen gastric ulcers in chicks, 532
- Chest: See Thorax
- Chickenpox, 158
- Chilblains; pernio, 461
- Children, acquired syphilis in, 854
- intensive arsenotherapy in infants and children, 882
- juvenile obesity, 1070
- Cholera, chemotherapy of, 137
- Choriomeningitis: See Meningitis
- Cinchophen and Cinchophen Derivatives, cinchophen gastric ulcers in chicks, 532
- Cirrrosis: See Liver
- Claudication; vasospastic disorders, 458
- Clinics, administration of clinics for pregnant women with syphilis, 909
- Clinton, E.: Clearance of diodrast, phenol-sulfonphthalein and inulin in hypertension and in nephritis, 935
- Cobb, S.: Review of neuropsychiatry for 1942, 1017
- Coccidioidosis; coccidioidomycosis, 171
- Cohn, C.: Sodium *d*-lactate tolerance as test of hepatic function, 829
- Cold: See also Temperature
- effect of, 460
- pressor phenomena, 482
- Colds: See Respiratory Tract, diseases
- Colitis, nonspecific ulcerative, 664

- Collen, M. F.: Interrelation of factors influencing mortality in diabetic coma; statistical study, 369  
Mortality in diabetic coma, 347  
Colon: See also Gastrointestinal Tract; Intestines  
cancer of colon and rectum, 669  
Colwell, A. R.: Observed course of diabetes mellitus and inferences concerning its origin and progress, 523  
Coma: See Diabetes Mellitus  
Communicable Diseases: See also Immunity; Meningitis; Syphilis; etc.  
infectious diseases; review of significant publications in 1941-1942, 132  
Congo Red Test: See Amyloidosis  
Cornea, Inflammation: See Keratitis  
Corsaro, J. F.: Mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975  
Cysts: See under names of organs and regions  
Dalton, J. W.: Critical statistical analysis of data on renal function in grouped subjects with essential hypertension, 948  
Dameshek, W.: Use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722  
Darling's Disease: See Histoplasmosis  
Dementia Paralytica, metrazol shock therapy of psychoses associated with dementia paralytica, 901  
de Takáts, G.: Vascular diseases; eighth annual review, 444  
Diabetes Insipidus, renal function in, 61  
Diabetes Mellitus: See also Blood sugar  
interrelation of factors influencing mortality in diabetic coma; statistical study, 369  
mortality in diabetic coma, 347  
observed course and inferences concerning its origin and progress, 523  
unusually high insulin requirements in; report of case, 221  
Dickes, R.: Multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121  
Diet and Dietetics: See also Nutrition; Vitamins; etc.  
diet prescriptions in obesity, 1093  
Digestive System: See Gastrointestinal Tract; Intestines; Stomach; etc.  
Diodrast: See Iodine and Iodine Preparations  
Diphtheria, 147  
Disease, neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236  
Diuresis and Diuretics: See also Diabetes Insipidus; Kidneys  
mechanism of pentothal sodium antidiuresis, 567  
mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975  
renal function in diabetes insipidus, 61  
Diverticula: See under Intestines  
Drugs, sensitivity and meteorologic environment, 873  
Duodenum, effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959  
sphincter of Oddi, 636  
Ulcers: See Peptic Ulcer  
Dysentery, 146  
bacillary, and typhoid fever, chemotherapy of, 136  
Dyspnea of heart failure, 313.  
Edema, 476  
Editors, medical, meeting of, 344  
Edwards, J. C.: Clearance of diodrast, phenol-sulfonphthalein and inulin in hypertension and in nephritis, 935  
Electrocardiogram: See under Heart  
Electroencephalography: See under Brain  
Embolism: See also Thrombosis  
and thrombosis, 470  
arterial occlusions, 497  
Emotions; emotional craving for food, 1080  
Emphysema, experimental production of, 379  
Empyema, maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
pneumococcal, chemotherapy of, 133  
Encephalitis, 163  
Encephalography: See under Brain  
Endocarditis, bacterial, sulfonamide compounds in therapy; comparison of in vitro inhibitory effects and bacteriostatic activity, 777  
subacute bacterial, 329  
subacute bacterial, chemotherapy of, 133  
Endocrine Glands, endocrine disorders and obesity, 1058  
endocrine hypertension, 487  
endocrine medication of obesity, 1086  
internal secretions of gastrointestinal tract, 595  
Energy Exchange: See Metabolism  
Engel, G. L.: Neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236  
Enteritis: See Intestines, diseases  
Enterorrhagia: See Gastrointestinal Tract, hemorrhage  
Erythremia: See Polycythemia  
Esophagus, diseases of, 608  
hiatal esophageal hernia, 340  
multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121  
Estrogens, effect on syphilis, 840  
Exercise for obesity, 1086  
Exophthalmos in patients with various types of goiter, 206  
Extrapyramidal Tract, disorders of extrapyramidal system, 1022  
physiology of extrapyramidal system, 1024  
Extrasystoles: See Arrhythmia  
Extremities, Amputation: See Amputations  
Blood Supply, 448. See also Blood vessels; Embolism; Raynaud's Disease; Thromboangiitis obliterans; etc.  
blood supply; diagnostic tests, 454  
blood supply; effect of drugs, 456  
blood supply; treatment of peripheral vascular disease, 477  
blood supply; vascular diseases; eighth annual review, 444  
blood supply; vasomotor apparatus in peripheral vascular disease, 501  
Paralysis: See Poliomyelitis  
temperature studies, 447  
Eyes, syphilis and ophthalmic conditions, 888  
Favre-Nicolas' Disease: See Lymphogranuloma Venereum  
Feces, use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722  
Fellowships in medicine and public health, 343  
Fever: See also Malaria; Temperature; Typhoid; Typhus; etc.  
intermittent, of unknown origin; recurrent high fever with benign outcome in patient with migraine and notes on "neurogenic" fever, 293  
Therapeutic: See Neurosyphilis; Syphilis; etc.  
Flindley, T.: Clearance of diodrast, phenol-sulfonphthalein and inulin in hypertension and in nephritis, 935  
Finland, M.: Staphylococcal pneumonia occurring during epidemic of influenza, 183  
Flitz, R.: Polycythemia vera; report of case, 919  
Flint's Murmur: See under Heart  
Food: See also Diet and Dietetics; Nutrition; Vitamins; etc.  
emotional craving for, 1080  
habits of obese, 1082  
increased absorption of, 1054  
selection in obesity, 1088  
Franco, S. C.: Multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121  
Fungi; fungous and yeast infections, 170

- Ganglion**, basal ganglions and allied structures, 1023
- Gastric Julee**: See under Stomach
- Ulcer**: See Peptic Ulcer
- Gastritis**: See under Stomach
- Gastroenterology**; review of literature from July 1941 to July 1942, 585
- Gastrointestinal Tract**: See also Colon; Intestines; Rectum; Stomach; etc.
- absorption, 603
- diverticula and unusual tumors, 637
- function, 585
- hemorrhage; multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121
- internal secretions of, 595
- miscellaneous observations, 676
- specific infections, diagnosis and treatment, 652
- syphilis and gastrointestinal disorders, 886
- war medicine, 682
- Gastroscopy**: See Stomach
- Genitals**, syphilis and genital lesions in female due to other diseases, 914
- Glass, W. I.**: Unusually high insulin requirements in diabetes mellitus; report of case, 221
- Glomerulonephritis**: See under Nephritis
- Golter**: See also Thyroid
- exophthalmos in patients with various types of golter, 206
- Gold, H.**: Anthrax; review of 60 cases, with report on therapeutic use of sulfonamide compounds, 785
- Goldman, D.**: Polymyositis; report of fatal case, 822
- Goodman, J. I.**: Mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975
- Gordon, W. H.**: Gummatous aortitis, 396
- Gout**, uric acid partition in gout and in hepatic disease, 101
- Gramicidin**, antibiotic agents, 175
- Granuloma**, Coecidoidai: See Coecidoidosis
- Graybiel, A.**: Diseases of heart; review of significant contributions made during 1941, 303
- Grishman, E.**: Uric acid partition in gout and in hepatic disease, 101
- Haemophilus Influenzae**: See Influenza
- Harmon, P. H.**: Congo red test for amyloid disease; quantitative technic, 416
- Utility of congo red test in diagnosis and in differential diagnosis, 421
- Havens, W. P.**: Etiology of atypical ("virus") pneumonias with brief résumé of recent discoveries, 513
- Hodgkin's disease with specific lesions appearing first in skin, 434
- Heart**: See also Arrhythmia; Cardiovascular System; Endocarditis; Myocarditis; etc.
- bloek; Stokes-Adams attacks, 323
- congenital heart disease, 325
- Diseases: See also Endocarditis; Myocarditis; etc.
- diseases; review of significant contributions made during 1941, 303
- dyspnea of heart failure, 313
- electrocardiographic abnormalities associated with massive dose arsenotherapy, 882
- electrocardiographic changes in rheumatic fever, 328
- electrocardiography, 318
- Flint's murmur, 892
- in wartime with reference to neurocirculatory asthenia, 303
- incomplete rupture of aorta; heretofore unrecognized stage of dissecting aneurysm and cause of cardiac pain and cardiac murmurs, 689
- infarction in syphilitic heart disease, 893
- mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975
- Heart—Continued**
- production and study of cardiac failure in thiamine-deficient pigeons, 763
- stenosis of infundibulum, 53
- thrombosis, 341
- tuberculosis, 331
- Hecht, P.**: Maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749
- Hematemesis**, multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121
- Hematology**: See Blood
- Hemoglobin and Hemoglobin Compounds**: See also Anemia; Blood
- use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722
- Hemolysis**, use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722
- Hemorrhage**: See Gastrointestinal Tract
- Hensel, H. M.**: Maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749
- Hepatitis**: See under Liver
- Herbut, P. A.**: Hodgkin's disease with specific lesions appearing first in skin, 434
- Hernia**, diaphragmatic, 610
- hiatus esophageal hernia, 340
- Histoplasmosis**; fungous and yeast infections, 170
- Hodgkin's Disease** with specific lesions appearing first in skin, 434
- Hormones**: See Endocrine Glands; Estrogens; Insulin; etc.
- Horn, H.**: Vascular phase of chronic diffuse glomerulonephritis; clinicopathologic study, 260
- Hunger and appetite**, 1076
- Hyperpnea**: See under Respiration
- Hypertension**: See Blood pressure, high
- Hyperthyroidism**: See Thyroid, hyperthyroidism
- Hypertrophy**: See under names of organs and regions
- Hypoglycemia**: See Blood sugar
- Hypophysis**: See Pituitary Body
- Hypotension**: See Blood pressure, low
- Hypothalamus**: See also Pituitary Body and obesity, 1068
- Icterus**: See Jaundice
- Immunity**; immune reactions, 176
- Industrial Diseases**, acute coronary thrombosis in industry; direct nonpenetrating injuries with report of cases, 33; correction, 686
- syphilis and industry, 862
- Infantile Paralysis**: See Poliomyelitis
- Infarction**: See under Heart
- Infection**: See also under names of bacteria, as Staphylococci; Streptococci; etc.
- infectious diseases; review of significant publications in 1941-1942, 132
- miscellaneous diseases, 172
- Infectious Diseases**: See Communicable Diseases
- Influenza**, 151
- and colds, 151
- staphylococcal pneumonia occurring during epidemic of, 183
- vaccine, 152
- Infundibulum**: See under Heart
- Insulin**: See also Diabetes Mellitus
- unusually high insulin requirements in diabetes mellitus; report of case, 221
- Internal Secretions**: See Endocrine Glands
- Intestines**: See also Colon; Duodenum; Gastrointestinal Tract; Rectum
- Diseases: See also Dysentery
- diseases; regional enteritis, 662
- diverticula and unusual tumors, 637
- obstruction, 643
- parasitic diseases, 650

- Inulin, clearance of diodrast, phenolsulfonphthalein and inulin in hypertension and in nephritis, 935
- Iodine and Iodine Compounds, clearance of diodrast, phenolsulfonphthalein and inulin in hypertension and in nephritis, 935
- Iron Therapy: See under Anemia
- Jaundice, sodium *d*-lactate tolerance as test of hepatic function, 829
- Jenkins, J. A.: Control by radium for gastric acidity, 714
- Joints, syphilis and orthopedic conditions, 888
- Jones, C. M.: Gastroenterology; review of literature from July 1941 to July 1942, 585
- Journals: See Periodicals
- Jurisprudence, Medical; legal aspects of syphilis and pregnancy, 908
- Keratitis, interstitial, 912
- Kernwein, G.: Congo red test for amyloid disease; quantitative technic, 416  
Utility of congo red test in diagnosis and in differential diagnosis, 421
- Kidneys, clearance of diodrast, phenolsulfonphthalein and inulin in hypertension and in nephritis, 935  
counterpressor mechanism, 492  
critical statistical analysis of data on renal function in grouped subjects with essential hypertension, 948  
Diseases: See also Nephritis; Pyelonephritis  
function of separate kidneys in hypertensive subjects, 738  
renal function in diabetes insipidus, 61
- Klemperer, P.: Vascular phase of chronic diffuse glomerulonephritis; clinicopathologic study, 260
- Klendshoj, N. C.: Transfusion of conditioned universal blood; clinical observations, 1
- Knudsen, A. F.: Multiple polyps of esophagus; report of case with complicating recurrent gastrointestinal hemorrhages, 121
- Leinoff, H. D.: Acute coronary thrombosis in industry; direct nonpenetrating injuries with report of cases, 33; correction, 686
- Leprosy, 150
- Lev, M.: Stenosis of infundibulum, 53; correction, 686
- Lipophilia, 1054
- Liver, cirrhosis; maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
sodium *d*-lactate tolerance as test of hepatic function, 829  
uric acid partition in gout and in hepatic disease, 101
- Lumbar Puncture: See Spinal Puncture
- Lungs: See also Respiration; Respiratory Tract; Thorax; etc.  
acute disseminated lupus erythematosus without cutaneous manifestations and with heretofore undescribed pulmonary lesions, 88
- Lupus erythematosus, acute disseminated, without cutaneous manifestations and with heretofore undescribed pulmonary lesions, 88  
erythematosus, disseminated, 340
- Luxuskonsumption, 1041
- Lymphocytes in Meningitis: See Meningitis
- Lymphogranuloma: See Hodgkin's Disease
- Lymphogranuloma Venereum and syphilis, 913  
false positive serologic reactions associated with lymphogranuloma venereum, 851
- McGeorge, M.: Control by radium for gastric acidity, 714
- McNell, C.: Transfusion of conditioned universal blood; clinical observations, 1
- Malaria, 169  
chemotherapy of, 898  
false positive serologic reactions associated with malaria, 850  
Therapeutic: See Neurosyphilis
- Marcus, P. L.: Vascular diseases; eighth annual review, 444
- Margolin, S. G.: Neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236
- Mediastinum, aortic aneurysm as cause of obstruction of venous circulation of mediastinum, 893
- Medicine, announcement of fellowships in medicine and public health, 343  
internal; neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236
- Medicine, Military: See also Recruits  
prostitution, 856  
syphilis in armed forces, 859  
venereal disease control officers in armed services, 861  
war medicine, 682  
wartime problems of civilian public health agencies, 855
- Medicine, Naval; syphilis in armed forces, 859
- Meninges, permeability; barrier between blood and brain, 906
- Meningitis: See also Meningococci  
chemotherapy of, 135  
lymphocytic choriomeningitis, 165
- Meningococci, 146. See also under Meningitis
- Mercury; mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975
- Metabolism, basal, 1035  
neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236  
total, 1044
- Meteorology, drug sensitivity and meteorologic environment, 873
- Metrazol, Therapy: See Dementia Paralytica
- Migraine, intermittent fever of unknown origin; recurrent high fever with benign outcome in patient with migraine and notes on "neurogenic" fever, 293
- Miller, E. B.: Use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722
- Mind, psychosomatics, 1019
- Mohr, C. F.: Syphilis; review of recent literature, 836
- Mononucleosis, infectious, associated with false positive serologic reactions, 851
- Moore, J. E.: Syphilis; review of recent literature, 836
- Mouth, diseases of, 607
- Movements, involuntary, therapy of, 1027
- Myers, G. B.: Treatment of pneumonia with sulfathiazole, 558
- Myocarditis, syphilitic, 893
- National Defense: See War
- Navies: See Medicine, Naval
- Negroes, syphilis in, 854
- Nephritis: See also Pyelonephritis  
clearance of diodrast, phenolsulfonphthalein and inulin in hypertension and in nephritis, 935  
maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
vascular phase of chronic diffuse glomerulonephritis; clinicopathologic study, 260
- Nerves: See Nervous System; Neuritis
- Nervous System: See also Brain; Spinal Cord; etc.  
gastrointestinal function, 585  
Syphilis: See Neurosyphilis  
Neuritis, syphilitic trigeminal neuritis, 895
- Neuropsychiatry, neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236  
review for 1942, 1017
- Neuroses and Psychoneuroses; intermittent fever of unknown origin; recurrent high fever with benign outcome in patient with migraine and notes on "neurogenic" fever, 293

- Neurosyphilis, artificial fever therapy, 898  
 encephalographic studies, 896  
 malaria inoculata in therapy, 897  
 management of, 894  
 syphilis of central nervous system, 894  
 Newburgh, L. H.: Obesity, 1033  
 Nicolas-Favre's Disease: See Lymphogranuloma Venereum  
 Nitrogen, maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
 Nutrition: See Diet and Dietetics; Food; Vitamins; etc.  
 Nuzum, F. R.: Critical statistical analysis of data on renal function in grouped subjects with essential hypertension, 948
- Obesity, 1033**  
 and hypoglycemia, 1083  
 and hypothalamus, 1068  
 and pituitary body, 1061  
 and specific dynamic effect, 1039  
 and thyroid, 1058  
 diet in, 1088  
 diet prescriptions, 1093  
 endocrine medication, 1086  
 etiology of, 1034  
 exercise for, 1086  
 food habits of obese, 1082  
 fundamental cause of, 1084  
 heredity, 1073  
 increased absorption of food, 1054  
 juvenile, 1070  
 prevention, 1085  
 selection of food, 1088  
 treatment, 1086
- Occupational Diseases: See Industrial Diseases  
 Optic Chiasm; surgical treatment of optic chiasm arachnoiditis, 905  
 Orchiectomy: See Testes  
 Orgain, E. S.: Sulfonamide compounds in therapy of bacterial endocarditis: comparison of in vitro inhibitory effects and bacteriostatic activity, 777  
 Oxygen, deficiency; hyperpnea of anoxemia, 313  
 deficiency; induced anoxemia in patients with coronary arteriosclerotic heart disease, 337  
 neuropsychiatric disturbances in internal disease; metabolic factors and electroencephalographic correlations, 236
- Pain, incomplete rupture of aorta; heretofore unrecognized stage of dissecting aneurysm and cause of cardiac pain and cardiac murmurs, 689  
 Paralysis, General: See Dementia Paralytica  
 Infantile: See Poliomyelitis  
 Parasites, parasitic diseases, 650  
 Parker, F., Jr.: Gummatous aortitis, 396  
 Peery, T. M.: Incomplete rupture of aorta; heretofore unrecognized stage of dissecting aneurysm and cause of cardiac pain and cardiac murmurs, 689  
 Pentothal Sodium: See Anesthesia  
 Peptic Ulcer, 620  
 cinchophen gastric ulcers in chicks, 532  
 control by radium for gastric acidity, 714  
 effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959  
 Perlarthritis nodosa, 474  
 Periodicals, Proceedings of Federation of American Societies for Experimental Biology, 343, 511  
 Perno: See Chills  
 Peterson, O. L.: Staphylococcal pneumonia occurring during epidemic of influenza, 183  
 Phenolsulfonphthalein, clearance of diodrast, phenolsulfonphthalein and inulin in hypertension and in nephritis, 935  
 Pinta and bejel, 843  
 Pituitary Body: See also Hypothalamus  
 and obesity, 1061  
 Pituitary Preparations, renal function in diabetes insipidus, 61  
 Plague, 149
- Pneumococci: See Pneumonia  
 Pneumonia, etiology of atypical ("virus") pneumonias with brief résumé of recent discoveries, 513  
 other forms of, 143  
 pneumococcal, 141  
 rheumatic, 327  
 staphylococcal, occurring during epidemic of influenza, 183  
 treatment with sulfathiazole, 558  
 "virus" pneumonia, 156  
 Poisons and Poisoning: See under names of substances, as Carbon Monoxide; etc.  
 Poliomyelitis, 159  
 Pollack, H.: Unusually high insulin requirements in diabetes mellitus; report of case, 221  
 Polycythemia vera; report of case, 919  
 Polymyositis; report of fatal case, 822  
 Polyps: See Esophagus  
 Polyuria: See Diabetes Insipidus  
 Position: See Posture  
 Poston, M. A.: Sulfonamide compounds in therapy of bacterial endocarditis; comparison of in vitro inhibitory effects and bacteriostatic activity, 777  
 Posture, orthostatic circulatory insufficiency in tabes dorsalis, 905  
 Pregnancy, administration of clinics for pregnant women with syphilis, 909  
 and syphilis, 907  
 legal aspects of syphilis and pregnancy, 908  
 Price, A. E.: Treatment of pneumonia with sulfathiazole, 558  
 Price, A. H.: Etiology of atypical ("virus") pneumonias with brief résumé of recent discoveries, 513  
 Prostitution, 856  
 Proteins in Cerebrospinal Fluid: See under Cerebrospinal Fluid  
 Psychoneurosis: See Neuroses and Psychoneuroses  
 Public Health, announcement of fellowships in medicine and public health, 343  
 wartime problems of civilian public health agencies, 855  
 Pulse: See also Arrhythmia; Blood pressure; Heart  
 rate in acute rheumatism, 327  
 Pursley, R.: Maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
 Pyelonephritis and hypertension; study of their relation in 11,898 necropsies, 284
- Radium, control for gastric acidity, 714  
 Rakov, H. L.: Acute disseminated lupus erythematosus without cutaneous manifestations and with heretofore undescribed pulmonary lesions, 88  
 Rasmussen, R. A.: Experimental production of emphysema, 379  
 Rat Bite Fever, 168  
 associated with false positive serologic reactions, 851  
 Raynaud's Disease, 462  
 Recruits, rehabilitation of men rejected because of venereal disease, 858  
 syphilis among selectees, 857  
 Rectum, cancer of colon and rectum, 669  
 Redish, J.: Function of separate kidneys in hypertensive subjects, 738  
 Reflex, Carotid Sinus: See Carotid Sinus  
 Rehfuess, M. E.: Effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959  
 Reimann, H. A.: Etiology of atypical ("virus") pneumonias with brief résumé of recent discoveries, 513  
 Hodgkin's disease with specific lesions appearing first in skin, 434  
 Infectious diseases; review of significant publications in 1941-1942, 132  
 Respiration, anesthesia and depression of respiratory center, 314  
 Cheyne-Stokes, 313  
 hyperpnea of anoxemia, 313

- Respiration—Continued  
 physiology of, 311  
 respiratory center, 312
- Respiratory Tract, diseases; colds and influenza, 151
- Reynolds, F. W.: Syphilis; review of recent literature, 836
- Rheumatic Fever, chemotherapy of, 136  
 complications, 328  
 electrocardiographic changes, 328  
 pulse rate in acute rheumatism, 327  
 rheumatic heart disease, 326  
 rheumatic pneumonia, 327  
 syphilis and rheumatic heart disease, 914  
 treatment, 329
- Rickettsia: See also Rocky Mountain Spotted Fever; Typhus  
 rickettsial disease, 166
- Rocky Mountain Spotted Fever, 166
- Roentgen Rays, Therapy: See Thyroid, hyperthyroidism
- Scarlet Fever, 330. See also Streptococci  
 chemotherapy of, 135
- Scupham, G. W.: Vascular diseases; eighth annual review, 444
- Secretions, Internal: See Endocrine Glands
- Semen, infectiousness of rabbit semen, 842
- Serum: See Blood
- Sharpe, J. C.: Refractory hemolytic anemia; report of 5 cases in which treatment was with splenectomy, 11
- Shigella Dysenteriae: See Dysentery
- Shure, N. M.: Pyelonephritis and hypertension; study of their relation in 11,898 necropsies, 284
- Sigler, L. H.: Hyperactive vasodepressor carotid sinus reflex, 983
- Slivette, H.: Mechanism of pentothal sodium antiduresis, 567
- Singer, K.: Use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722
- Sinus, Carotid: See Carotid Sinus
- Skin, capillaries, 445  
 effect of cold, 460  
 Hodgkin's disease with specific lesions appearing first in skin, 434  
 temperature studies, 447
- Sobotka, H.: Uric acid partition in gout and in hepatic disease, 101
- Societies, American Association for Advancement of Oral Diagnosis, 178, 344, 511, 686  
 American College of Physicians, 178, 1097  
 Chicago Society of Internal Medicine, 178  
 meeting of medical editors, 344  
 Mississippi Valley Medical Society, 343
- Sodium *D*-Lactate: See under Blood
- Solcy, M. H.: Exophthalmos in patients with various types of goiter, 206  
 Roentgen ray treatment of hyperthyroidism, 1002
- Spasm, therapy of involuntary movements, 1027
- Sphincter Muscles; duodenum (sphincter of Oddi), 636
- Spinal Cord: See also Meninges; Nervous System; etc.  
 degeneration produced experimentally by dietary means, 902  
 syphilis, 895
- Spinal Fluid: See Cerebrospinal Fluid
- Spinal Puncture; injury to intervertebral disk from lumbar puncture, 906
- Spine, injury to intervertebral disk from lumbar puncture, 906
- Spingarn, C. L.: Unusually high insulin requirements in diabetes mellitus; report of case, 221
- Spirochaeta Pallida, 838. See also Syphilis  
 dispersion in mice, 840
- Spirochetosis; Weil's disease, 168
- Spleen, utility of congo red test in diagnosis and in differential diagnosis, 421
- Splenectomy, refractory hemolytic anemia; report of 5 cases in which treatment was with splenectomy, 11
- Stacy, R.: Mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975
- Staphylococci, infection, 145  
 infections, chemotherapy of, 134  
 staphylococcal pneumonia occurring during epidemic of influenza, 183
- Steinberg, M. F.: Vascular phase of chronic diffuse glomerulonephritis; clinicopathologic study, 260
- Stomach: See also Gastrointestinal Tract  
 cancer, 633  
 control by radium for gastric acidity, 714  
 diverticula and unusual tumors, 637  
 effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959  
 gastric lesions of early syphilis, 876  
 gastritis and gastroscopy, 612  
 Ulcers: See Peptic Ulcer
- Stone, R. S.: Roentgen ray treatment of hyperthyroidism, 1002
- Stools: See Feces
- Strauss, E.: Staphylococcal pneumonia occurring during epidemic of influenza, 183
- Strauss, S.: Stenosis of infundibulum, 53; correction, 686
- Streptococci infection, 144
- Sugar in Blood: See Blood, sugar
- Sulfanilamide and Sulfanilamide Derivatives, drug fastness, 140  
 sulfonamide compounds in therapy of bacterial endocarditis; comparison of in vitro inhibitory effects and bacteriostatic activity, 777  
 Therapy: See Anthrax; Dysentery; Empyema; Endocarditis; Meningitis; Pneumonia; Rheumatic Fever; Scarlet Fever; etc.  
 untoward effects, 139
- Sulfathiazole: See Pneumonia
- Sulfonamide Compounds: See Anthrax; Sulfanilamide and Sulfanilamide Derivatives
- Swank, R. L.: Production and study of cardiac failure in thiamine-deficient pigeons, 763
- Swanson, P.: Transfusion of conditioned universal blood; clinical observations, 1
- Syphilis: See also under names of organs and regions, as Aorta; Bones; Cardiovascular System; Eyes; Spinal Cord; etc.; and under names of diseases, as Myocarditis; etc.  
 accidental inoculation, 839  
 acquired, in children, 854  
 administration of clinics for pregnant women with syphilis, 909  
 among selectees, 857  
 and gastrointestinal disorders, 886  
 and gynecologic disorders, 887  
 and industry, 862  
 and ophthalmic conditions, 888  
 and orthopedic conditions, 888  
 and other diseases, 913  
 and pregnancy, 907  
 and war, 855  
 arsenical sensitivity and ascorbic acid, 872  
 biologic false positive serologic reactions for, 848  
 combined fever therapy and chemotherapy, 900  
 combined therapy with fever and arsenicals, 880  
 congenital, 909  
 congenital, dental abnormalities associated with, 911  
 congenital, in third generation, 913  
 congenital, syphilitic aortitis in, 911  
 contact investigation, 855  
 drug sensitivity and meteorologic environment, 873  
 drugs for, 863  
 early, 854, 875  
 early, fever therapy of, 877  
 effect of estrogens, 840  
 effect of orchidectomy on immunity, 840  
 effect of treatment on results of quantitative serologic tests, 848

- Syphilis**—Continued  
 epidemiology of, 854  
 experimental, 839  
 gastric lesions, 876  
 Hereditary: See Syphilis, congenital  
 history of, 836  
 immunity to syphilitic infection, 839  
 in armed forces, 859  
 in Negroes, 854  
 infectious, relapse, 875  
 infectiousness of rabbit semen, 842  
 intensive arsenotherapy, 880  
 legal aspects of syphilis and pregnancy, 908  
 mortality data, 869  
 pinta and bejel, 843  
 prevalence, 852  
 review of recent literature, 836  
 serodiagnosis of, 844  
 storage of serums, 848  
 tests purported to "verify" results of standard serodiagnostic tests, 851  
 treatment, 869  
 untoward effects of treatment, 869  
 uveitis due to, 876  
 wartime problems of civilian public health agencies, 855
- Tabes Dorsalis**: See also Neurosyphilis  
 neurogenic bladder, 903  
 orthostatic circulatory insufficiency in, 905  
 vitamin therapy of, 902
- Taylor, J. S.**: Acute disseminated lupus erythematosus without cutaneous manifestations and with heretofore undescribed pulmonary lesions, 88
- Teeth**, dental abnormalities associated with congenital syphilis, 911
- Temperature**: See also Cold  
 temperature studies, 447
- Testes**, effect of orchidectomy on immunity to syphilis, 840
- Tetanus**, 148
- Thiamine**, production and study of cardiac failure in thiamine-deficient pigeons, 763
- Thomas, J. E.**: Effect of ulcer on acidity and neutralizing ability in duodenal bulb, 959
- Thorax**: See also Heart; Lungs; Mediastinum; etc.  
 acute coronary thrombosis in industry; direct nonpenetrating injuries with report of cases, 33; correction, 686  
 Thromboangitis obliterans, 472  
 Thrombosis: See also Embolism  
 acute coronary thrombosis in industry; direct nonpenetrating injuries with report of cases, 33; correction, 686  
 and embolism, 470  
 arterial occlusions, 497  
 precipitating factors in coronary occlusion, 336  
 thrombi in heart, 341  
 venous, 495
- Thyroid**: See also Goiter  
 and obesity, 1058  
 hyperthyroidism; roentgen ray treatment, 1002  
 maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749
- Toifman, J. P.**: Refractory hemolytic anemia; report of 5 cases in which treatment was with splenectomy, 11
- Trauma**, acute coronary thrombosis in industry; direct nonpenetrating injuries with report of cases, 33; correction, 686
- Tremor**, therapy of involuntary movements, 1027
- Tuberculosis**: See also under Heart  
 experimental, arspenamine in treatment, 841
- Tularemia**, 149
- Tumors**: See also under Gastrointestinal Tract; etc.  
 maintenance of nitrogen equilibrium by intravenous administration of amino acids; clinical studies, 749  
 vascular, 475
- Typhoid**, 147  
 and bacillary dysentery, chemotherapy of, 136
- Typhus**, 166
- Ulcers**, Peptic: See Peptic Ulcer
- Unconsciousness**, interrelation of factors influencing mortality in diabetic coma; statistical study, 369
- Uric Acid in Gout**: See Gout
- Urine**: See also Diuresis and Diuretics; etc.  
 suppression; mechanism of pentothal sodium antidiuresis, 567
- Urobilinogen**, use of daily fecal output of urobilinogen and hemolytic index in measurement of hemolysis, 722
- Uvea**; uveitis due to syphilis, 876
- Vaccine Therapy**: See Influenza
- Valley Fever**: See Coccidioidosis
- Van Deilen, T. R.**: Vascular diseases; eighth annual review, 444
- Vasomotor System**: See also Arteries; Blood vessels; etc.  
 hyperactive vasodepressor carotid sinus reflex, 983  
 vasomotor apparatus in peripheral vascular disease, 501  
 vasospastic disorders, 458
- Veneral Diseases**: See also Neurosyphilis; Syphilis  
 control officers in armed services, 861  
 rehabilitation of men rejected because of, 858
- Venous Pressure**: See Blood pressure
- Viruses**, etiology of atypical ("virus") pneumonias with brief résumé of recent discoveries, 513  
 virus diseases, chemotherapy of, 138  
 "virus" pneumonia, 156
- Vitamins**: See also Ascorbic Acid; Thiamine  
 B<sub>1</sub>: See Thiamine  
 C: See Ascorbic Acid  
 degeneration of spinal cord produced experimentally by dietary means, 902  
 therapy of tabes dorsalis, 902
- Walker, B. S.**: Polycythaemia vera; report of case, 919
- War**: See also Medicine, Military; Medicine, Naval; Wounds; etc.  
 and syphilis, 855  
 heart in wartime with reference to neurocirculatory asthenia, 303  
 wartime problems of civilian public health agencies, 855
- Wassermann Reaction**, antigen, 844
- Water balance**, 1050
- Weight**, hazard of overweight, 1033  
 normal, 1033
- Weil's Disease**: See Spirochetosis
- Weiss, S.**: Gummatous aortitis, 396
- White, H. L.**: Clearance of diodrast, phenol-sulfonaphthalein and inulin in hypertension and in nephritis, 935
- White, P. D.**: Diseases of heart; review of significant contributions made during 1941, 303
- Winer, N. J.**: Renal function in diabetes insipidus, 61
- Witebsky, E.**: Transfusion of conditioned universal blood; clinical observations, 1
- Wolf, S.**: Intermittent fever of unknown origin; recurrent high fever with benign outcome in patient with migraine and notes on "neurogenic" fever, 293
- Wolff, H. G.**: Intermittent fever of unknown origin; recurrent high fever with benign outcome in patient with migraine and notes on "neurogenic" fever, 293
- Wounds**, syphilis and gynecologic disorders, 887
- Xanthine**, mercurial and xanthine diuretics in chronic congestive heart failure; comparative survey, 975
- Yeast**; fungous and yeast infections, 170
- Yellow Fever**, 165

